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Ketamine Versus Midazolam for Prehospital Agitation

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ClinicalTrials.gov Identifier: NCT03554915

Recruitment Status: Recruiting
First Posted: June 13, 2018
Last Update Posted: June 13, 2018

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Sponsor:
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Study Description

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Brief Summary:
This research study is being done to figure out the best approach to treatment of pre-hospital agitation. It will compare two tiered dosing treatment protocols, one ketamine-based and one midazolam-based. Agitation is a state of extreme emotional disturbance where patients can become physically aggressive or violent, endangering themselves and those who are caring for them. Often chemical substances or severe mental illness are involved in this level of agitation. Specifically, the investigators are interested in studying agitation that is treated in the prehospital setting by paramedics. This study's hypothesis is a ketamine-based protocol will achieve a faster time to adequate sedation than a midazolam-based protocol for treatment of agitation in the prehospital environment. This study will observe the natural history of an emergency medical services standard operating procedure change from a ketamine-based protocol to a midazolam-based protocol.

Condition or disease	Intervention/treatment	Phase
Agitation	Other: Ketamine-based protocol Other: Midazolam-based protocol	Phase 4

Study Design

Study Type: Interventional (Clinical Trial)
Estimated Enrollment: 420 participants

Allocation:	Non-Randomized
Intervention Model:	Sequential Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Ketamine Versus Midazolam for Prehospital Agitation
Actual Study Start Date:	August 1, 2017
Estimated Primary Completion Date:	August 31, 2018
Estimated Study Completion Date:	August 31, 2018

Resource links provided by the National Library of Medicine NIH NLM

Drug Information available for: Ketamine Midazolam Midazolam maleate Midazolam hydrochloride

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Active Comparator: Ketamine-based Protocol The first 6 month period of the study will employ a ketamine-based protocol for prehospital agitation. There will be a tiered dosing protocol based on degree of agitation.	Other: Ketamine-based protocol For profoundly agitated (physically violent) patients, intramuscular ketamine 5 mg/kg will be administered first line. For severely agitated patients, intramuscular ketamine 3 mg/kg will be administered first line.
Active Comparator: Midazolam-based Protocol The second 6 month period of the study will employ a midazolam-based protocol for prehospital agitation. There will again be a tiered dosing protocol based on degree of agitation.	Other: Midazolam-based protocol For profoundly agitated patients, intramuscular midazolam 15 mg will be administered. For severely agitated patients, intramuscular midazolam 5 mg will be administered.

Outcome Measures

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Primary Outcome Measures:

1. Time from injection of drug to adequate sedation, defined as a score of +1 or less on the AMSS [Time Frame: 2 hours]

   The Altered Mental Status Scale (AMSS) is an integral ordinal scale evaluating both agitation and sedation with scores from -4 to +4. It was developed at our institution and has been internally and externally validated. This scale is a modified version of the Behavioral Activity Rating Scale with additional data points from the Observer's Assessment of Alertness Scale. Effectiveness of sedation will be defined as an AMSS score less than or equal to +1.

   AMSS will be determined by the treating paramedic, who will undergo training as a research associate prior to commencement of the study. Participants will be followed for the duration of agitation, an expected average of 2 hours.

Secondary Outcome Measures:

1. Number of participants intubated [Time Frame: 2 hours]

Participants will be followed for the duration of agitation, an expected average of 2 hours. Enrolling paramedics or research associates in the Emergency Department will record if the patient is intubated.

2. Number of participants experiencing hypersalivation [Time Frame: 2 hours]

   Participants will be followed for the duration of agitation, an expected average of 2 hours. Enrolling paramedics or research associates in the Emergency Department will record if the patient experiences hypersalivation.

3. Number of participants experiencing apnea [Time Frame: 2 hours]

   Participants will be followed for the duration of agitation, an expected average of 2 hours. Enrolling paramedics or research associates in the Emergency Department will record if the patient experiences apnea, defined as 6 seconds of absent EtCO2 waveform.

4. Number of participants experiencing nausea/vomiting [Time Frame: 2 hours]

   Participants will be followed for the duration of agitation, an expected average of 2 hours. Enrolling paramedics or research associates in the Emergency Department will record if the patient experiences nausea/vomiting

5. Number of participants experiencing laryngospasm [Time Frame: 2 hours]

   Participants will be followed for the duration of agitation, an expected average of 2 hours. Enrolling paramedics or research associates in the Emergency Department will record if laryngospasm occurs.

6. Number of participants needing rescue sedation [Time Frame: 2 hours]

   Participants will be followed for the duration of agitation, an expected average of 2 hours. Enrolling paramedics or research associates in the Emergency Department will record if additional sedatives are needed in the prehospital or ED environment.

Eligibility Criteria

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Information from the National Library of Medicine

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Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Age 18 or older
- Severe agitation (AMSS +2 or +3) or profound agitation (AMSS +4) requiring chemical sedation
- Transport to Hennepin County Medical Center

Exclusion Criteria:

- Obviously gravid women
- Patients known or suspected to be less than 18 years of age
- Patients in which stopwatch activation, for safety reasons, is unable to occur

Contacts and Locations

Go to

Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT03554915***

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Locations

United States, Minnesota

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Sponsors and Collaborators

Minneapolis Medical Research Foundation

More Information

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Publications:

Cole JB, Klein LR, Nystrom PC, Moore JC, Driver BE, Fryza BJ, Harrington J, Ho JD. A prospective study of ketamine as primary therapy for prehospital profound agitation. Am J Emerg Med. 2018 May;36(5):789-796. doi: 10.1016/j.ajem.2017.10.022. Epub 2017 Oct 7.

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Other Study ID Numbers: HSR #17-4306
First Posted: June 13, 2018 Key Record Dates
Last Update Posted: June 13, 2018
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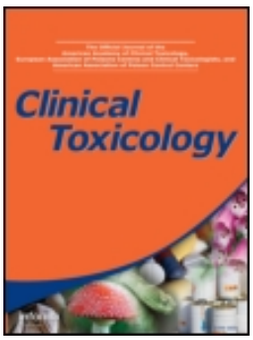
Plan to Share IPD: No

Studies a U.S. FDA-regulated Drug Product: No
Studies a U.S. FDA-regulated Device Product: No

Keywords provided by Minneapolis Medical Research Foundation:
Agitation, Ketamine, Midazolam, Emergency Medical Services

Additional relevant MeSH terms:

Psychomotor Agitation
Dyskinesias
Neurologic Manifestations
Nervous System Diseases
Psychomotor Disorders
Neurobehavioral Manifestations
Signs and Symptoms
Ketamine
Midazolam
Analgesics
Sensory System Agents
Peripheral Nervous System Agents
Physiological Effects of Drugs
Anesthetics, Dissociative
Anesthetics, Intravenous
Anesthetics, General
Anesthetics
Central Nervous System Depressants
Excitatory Amino Acid Antagonists
Excitatory Amino Acid Agents
Neurotransmitter Agents
Molecular Mechanisms of Pharmacological Action
Adjuvants, Anesthesia
Hypnotics and Sedatives
Anti-Anxiety Agents
Tranquilizing Agents
Psychotropic Drugs
GABA Modulators
GABA Agents



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A prospective study of ketamine versus haloperidol for severe prehospital agitation

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CLINICAL RESEARCH

A prospective study of ketamine versus haloperidol for severe prehospital agitation

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ABSTRACT

Context: Ketamine is an emerging drug for the treatment of acute undifferentiated agitation in the prehospital environment, however no prospective comparative studies have evaluated its effectiveness or safety in this clinical setting. **Objective:** We hypothesized 5 mg/kg of intramuscular ketamine would be superior to 10 mg of intramuscular haloperidol for severe prehospital agitation, with time to adequate sedation as the primary outcome measure. **Methods:** This was a prospective open label study of all patients in an urban EMS system requiring chemical sedation for severe acute undifferentiated agitation that were subsequently transported to the EMS system's primary Emergency Department. All paramedics were trained in the Altered Mental Status Scale and prospectively recorded agitation scores on all patients. Two 6-month periods where either ketamine or haloperidol was the first-line therapy for severe agitation were prospectively compared primarily for time to adequate sedation. Secondary outcomes included laboratory data and adverse medication events. **Results:** 146 subjects were enrolled; 64 received ketamine, 82 received haloperidol. Median time to adequate sedation for the ketamine group was 5 minutes (range 0.4–23) vs. 17 minutes (range 2–84) in the haloperidol group (difference 12 minutes, 95% CI 9–15). Complications occurred in 49% (27/55) of patients receiving ketamine vs. 5% (4/82) in the haloperidol group. Complications specific to the ketamine group included hypersalivation (21/56, 38%), emergence reaction (5/52, 10%), vomiting (5/57, 9%), and laryngospasm (3/55, 5%). Intubation was also significantly higher in the ketamine group; 39% of patients receiving ketamine were intubated vs. 4% of patients receiving haloperidol. **Conclusions:** Ketamine is superior to haloperidol in terms of time to adequate sedation for severe prehospital acute undifferentiated agitation, but is associated with more complications and a higher intubation rate.

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Agitation; EMS; haloperidol; ketamine

Introduction

Acute undifferentiated agitation is a commonly encountered problem in the prehospital environment [1] that represents risk for both the patient and caregivers. Data suggest over one third of Emergency Medical Technician (EMT) occupational injuries are patient related,[2] and for patients, severe agitation can culminate in profound metabolic abnormalities and even death.[3] Drug and alcohol intoxication is common in this patient population; one study found the presence of alcohol or intoxicating drugs to be in excess of 80% in these patients.[4] Chemical sedation has been shown to reduce agitation in the prehospital environment,[5], though the optimal agent has not been agreed upon. Traditional pharmacologic treatment of acute undifferentiated agitation in the prehospital environment has included butyrophenones such as droperidol and haloperidol [6–8] as well as benzodiazepines, typically midazolam.[4] Due to its rapid onset of action, tendency to preserve airway reflexes,[9] and reported wide therapeutic index,[10] ketamine has emerged as a promising therapy for acute undifferentiated agitation in the prehospital environment. Data describing its use however, are limited to case reports,[11,12] and case series.[13–15] Prospective comparative data on the use of ketamine for this indication is lacking.

The primary objective of this study was to determine if haloperidol or ketamine was superior for the treatment of severe prehospital acute undifferentiated agitation. Specifically, we hypothesized that in patients with severe agitation presenting to our EMS system, 5 mg/kg of intramuscular (IM) ketamine would be superior to 10 mg of IM haloperidol, with time to adequate sedation as our primary outcome measure. Secondary outcomes included need for redosing in the prehospital environment, the rate of adverse side effects, and rates of intubation between ketamine and haloperidol. Lastly, we investigated if this patient population could be feasibly consented to allow randomization in future studies.

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Methods

Study design and setting

This was a Waiver of Consent (45 CFR 46.116) [16] prospective observational study of patients with severe acute undifferentiated agitation within the EMS primary service area subsequently transported to the study hospital's Emergency Department (ED). This study was conducted at an urban Level 1 trauma center safety-net hospital with more than 110,000 annual ED visits starting with calls to its hospital-based EMS agency. The EMS agency responds to over 70,000 calls annually, serving an urban and suburban population of over 1,000,000 covering over 200 square miles. Approximately 500 patients per year receive chemical sedation by standing order protocol for "severe agitation." For the purpose of this study, "severe agitation" was defined as an Altered Mental Status Scale (AMSS) score of +2 or +3 (Table 1). All ambulances were staffed with two EMT-paramedics at all times. Mean scene time for the agency is 17.9 minutes; mean transport time is 12.2 minutes. All caregivers, both prehospital and in the ED, were unblinded to which medication the patients received.

Selection of participants

All patients in the EMS system with severe acute undifferentiated agitation subsequently transported to the study hospital were included in the study. Even in the instance where the etiology of the agitation was suspected, such as history of drug intoxication or overdose, patients were still included as diagnostic certainty was not possible in the prehospital environment. Exclusion criteria included obviously gravid women, persons who appeared or were known to be less than 18 years of age, and patients with "profound agitation," defined as an AMSS score of +4. Based on over 10 years of experience successfully treating profoundly agitated patients with ketamine,[17,18] our institution deemed it unethical and unwise to withhold ketamine from the most profoundly agitated patients at any time for both patient and caregiver safety.

Though this study was approved by the institutional IRB as a Waiver of Consent study, given the particularly vulnerable nature of this patient population a community consultation was performed in accordance with federal guidelines for Exception From Informed Consent (21 CFR 50.24) research.[19] Both the caregivers affected by this study as well as a select group of patients at a local homeless shelter's inpatient chemical dependency program were consulted. Details of the community consultation are available upon request.

Interventions

To minimize potential bias introduced by seasonal changes, data were collected throughout an entire calendar year. For the first three months of the study (October 2014–January 2015), the standard EMS operating procedure (SOP) for severely agitated patients was to treat acute undifferentiated agitation with 10 mg of IM haloperidol. For the next 6 months, haloperidol was removed from all ambulances in the system and the SOP for severely agitated patients was changed to 5 mg/kg of IM ketamine (dose calculation made by EMT-paramedic estimated weight in the field). For the final 3 months of the study, the SOP was returned to haloperidol 10 mg IM and haloperidol was reinstated on the ambulances. Doses for both drugs were chosen based on existing SOPs that had been in place since 2010. The ketamine dose was originally chosen based on procedural sedation dosing. A dose of 5 mg/kg was chosen because a lower dose, such as 3 mg/kg, may result in a partially dissociated state which would put both the patient and paramedics in further danger. Furthermore, the existing literature on ketamine advocates adverse events are not dose-dependent,[8,9] suggesting a higher dose poses little, if any, risk to the patient.

Methods and measurements

All paramedics were trained in the AMSS,[20] a validated score of agitation routinely used in agitation research at the study institution. Training was completed both online and at in-person training sessions led by the primary investigator. All paramedics were required to pass a quiz containing example patients where a correct AMSS score must be assigned. Upon encountering a patient with severe agitation requiring chemical sedation, paramedics activated a stopwatch immediately after injection of the sedative. Patients were excluded if stopwatch activation did not occur. AMSS scores were recorded every 5 minutes, or until adequate sedation was reached. Adequate sedation was defined clinically by the treating paramedic; however during training it was emphasized that adequate treatment of agitation would be an AMSS score $< +1$. Paramedics were specifically instructed to stop the stopwatch prior to 5 minutes if the patient appeared to have reached adequate sedation. Paramedics also recorded prospectively if a legally authorized representative was present at the scene to give consent.

Immediately upon arrival to the ED, paramedics transferred both the stopwatch and data collection form to research associates (RAs) who were trained in an identical manner in

Table 1. The altered mental status scale.

Score	Responsiveness	Speech	Facial Expression	Eyes
+4	Combative, very violent, or out of control	Loud outbursts	Agitated	Normal
+3	Very anxious, agitated, mild physical element of violence	Loud outbursts	Agitated	Normal
+2	Anxious, agitated	Loud outbursts	Normal	Normal
+1	Anxious, restless	Normal	Normal	Normal
0	Responds readily to name in normal tone	Normal	Normal	Clear, no ptosis
−1	Lethargic response to name	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (<half eye)
−2	Responds only if name is called loudly	Slurring or prominent slowing	Marked relaxation (slacked jaw)	Glazed and marked ptosis (>half eye)
−3	Responds only after mild prodding	Few recognizable words	Marked relaxation (slacked jaw)	Glazed and marked ptosis (>half eye)
−4	Does not respond to mild prodding or shaking	Few recognizable words	Marked relaxation (slacked jaw)	Glazed and marked ptosis (>half eye)

the AMSS. In the event adequate sedation was not reached prehospital, AMSS scores were recorded every 5 minutes in the ED until adequate sedation was reached. After reaching adequate sedation, stopwatch time was recorded. AMSS scores were subsequently recorded every 30 minutes by RAs until either hospital admission or discharge.

In addition to the parameters noted above, RAs also continually assessed real-time for airway and sedation complications based on previously defined definitions for our institution and research program.[21] If there was doubt about whether a specific complication occurred, RAs queried the treating physicians real time. RAs continually assessed for and recorded the need for additional sedatives, complications (specifically hypersalivation, emergence reaction, vomiting, dystonia, laryngospasm, akathisia, and death), intubation (including indications for intubation), history of mental illness or chemical dependency as recorded in the electronic medical record, vital signs, and laboratory data (if obtained) including breath ethanol concentration, serum ethanol concentration, venous pH, serum lactate, serum potassium, and urine drug screen results. Urine drug screens included a battery of 12 immunoassays in addition to liquid and gas chromatography capable of screening for over 1000 different compounds, though the vast majority of synthetic drugs were not detectable. Subjects were analyzed as intention to treat.

Analysis

Medians and ranges were calculated for the primary outcome, with the percentile difference and 95% confidence intervals calculated using the Hodges–Lehmann Estimation. Secondary outcomes of adequate sedation, complication rate and intubation rate were analyzed with a Chi-Square test and 95% confidence intervals for the difference between two proportions. Data were entered into Microsoft Excel 2010 and analyzed with Stata (StataCorp, College Station, TX). Descriptive statistics were used for the remaining variables.

Results

Characteristics of study subjects

A total of 146 patients were enrolled. Sixty-four patients received ketamine, 82 received haloperidol. For all enrolled subjects, median scene time was 22 minutes and median transport time was 8 minutes. Enrollment is delineated in Figure 1. Baseline demographics, vital signs, and laboratory values and ECG data were similar between groups (with the exception of the initial heart rate and systolic blood pressure) and are described in Tables 2 and 3. In the ketamine group, the median dose was 5.2 mg/kg IM (range 1.7–8.5). With the exception of a single patient, all patients in the ketamine group received at least 3 mg/kg. In the haloperidol group, 5 patients received an initial dose of 5 mg IM, the rest received 10 mg IM.

Legally authorized representatives (LARs) who could provide consent for the patient were present in only 6% of cases. In 82% of cases a LAR was not present to provide consent; in

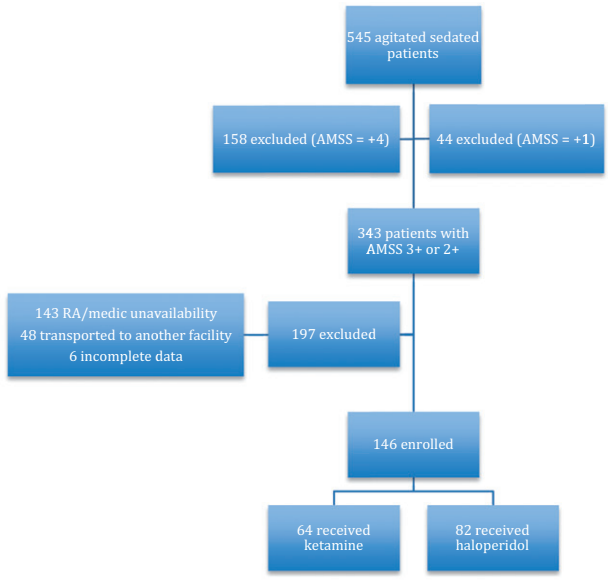

Figure 1. Patient enrollment.

Table 2. Demographics.

	Ketamine ($n = 64$)	Haloperidol ($n = 82$)
Initial AMSS (*n*)		
+3	57 (89%)	60 (73%)
+2	7 (11%)	22 (27%)
Age (median, years)	36 (range: 19–68)	31 (range: 18–69)
Gender (*n*)		
Male	37 (58%)	44 (54%)
Race (*n*)		
Caucasian	31 (48%)	33 (40%)
Black American	16 (25%)	25 (30%)
American Indian	7 (11%)	14 (17%)
Somali	3 (5%)	2 (2.5%)
Hispanic	2 (3%)	2 (2.5%)
Asian	1 (2%)	1 (1%)
Mixed/Unknown	4 (6%)	5 (6%)
History of Mental Illness (n)	48 (75%)	55 (67%)
Depression	19 (30%)	34 (41%)
Bipolar Disorder NOS	9 (14%)	8 (12%)
Anxiety Disorder NOS	8 (12%)	12 (15%)
Schizophrenia	3 (5%)	2 (2%)
Psychosis NOS	3 (5%)	3 (3.5%)
Schizoaffective Disorder	2 (3%)	3 (3.5%)
Cluster B Personality Disorder	2 (3%)	2 (2%)
Asperger syndrome	1 (1.5%)	0
Dementia	1 (1.5%)	0
Obsessive Compulsive Disorder	1 (1.5%)	0
Post-traumatic Stress Disorder	0	7 (8%)
Traumatic Brain Injury	0	3 (3.5%)
Fetal Alcohol Syndrome	0	1 (1%)
History of Chemical Dependency (n)	30 (47%)	59 (72%)
Chemical Dependency NOS	15 (23%)	12 (15%)
Alcohol abuse	9 (14%)	16 (20%)
Stimulant abuse	1 (1.5%)	2 (2%)
Opioid abuse	0	1 (1%)
History of both Mental Illness and Chemical Dependency (*n*)	25 (39%)	43 (52%)
Initial ED vital signs	Median (range)	Median (range)
Weight (kg)[a]	79.6 (47.1–147.6)	72.4 (61–100)
Heart rate (beats/min)	110 (57–158)	93 (62–154)
Systolic blood pressure (mmHg)	148 (67–205)	119 (77–179)
Respiratory rate (breaths/min)	17 (8–26)	16 (10–30)
Pulse oximetry (%)	97 (88–100)	96 (82–100)
Temperature (°C)	36.8 (33.9–40.3)	36.6 (35.6–38.3)

[a]Weights were only intermittently recorded ($n = 35$ for ketamine, $n = 7$ for haloperidol).

Table 3. Presenting ED laboratory and ECG data.

	Ketamine	Haloperidol
Median (range)		
Serum lactate (mmol/L)	2.6 (1.2–14.8) $n = 37$	2.4 (0.9–6.1) $n = 12$
Venous pH	7.34 (7.17–7.52) $n = 37$	7.38 (7.25–7.53) $n = 12$
Serum potassium (mmol/L)	3.7 (2.7–5.4) $n = 50$	3.6 (2.6–4.2) $n = 31$
Breath ethanol (mg/dL)	120 (0–340) $n = 23$	160 (0–490) $n = 70$
Serum ethanol (mg/dL)	220 (0–320) $n = 27$	0 (0–280) $n = 5$
QTc interval (miliseconds)[a]	414 (355–465) $n = 44$	418 (314–483) $n = 23$

[a]Computer calculation using Bazett's formula.

the remaining 12% of cases, it was not recorded if a LAR was present to give consent.

Main results

Time to adequate sedation was significantly faster in the ketamine group. Median time to adequate sedation for the ketamine group was 5 minutes (range 0.4–23) vs. 17 minutes (range 2–84) in the haloperidol group ($p < 0.0001$, difference 12 minutes, 95% CI: 9–15). Ninety-five percent (61/64) of patients in the ketamine group achieved adequate sedation prehospital compared to 65% (53/82) of patients in the haloperidol group ($p < 0.0001$, difference 0.3, 95% CI 0.18–0.42). Five percent of patients in the ketamine arm (3/64) required additional sedation prehospital (1 dose each of midazolam IM, ketamine IM, and ketamine IV) whereas 20% of patients in the haloperidol group required a second injection prehospital (15 doses of midazolam, 1 dose of haloperidol). The complication rate was significantly higher in the ketamine group. Complications occurred in 49% (27/55) of patients receiving ketamine vs. 5% (4/82) in the haloperidol group ($p < 0.0001$, difference 44%, 95% CI 0.3–0.57). Specific complications are delineated in Table 4. For patients who had a weight recorded ($n = 35$), median ketamine dose was 5.2 mg/kg ($n = 23$, range 4.0–8.5 mg/kg) in the group experiencing complications and 5.1 mg/kg ($n = 14$, range 1.7–6.25 mg/kg) in the group without complications.

Intubation rate was also significantly higher in the ketamine group; 39% (25/64) of patients receiving ketamine were intubated vs. 4% (3/82) of patients receiving haloperidol ($p < 0.0001$, difference 35%, 95% CI 23–48%). For intubated patients in the ketamine group who had a weight recorded ($n = 35$), median dose was 5.2 mg/kg ($n = 24$, range 4.0–8.5 mg/kg) in the intubated group and 5.1 mg/kg ($n = 13$, range 1.7–6.25 mg/kg) in the group not intubated. No intubations occurred prehospital. Primary indications for intubation as recorded by research associates upon querying the intubating physician are in Table 5. This table includes only the primary indication for intubation as assigned by the intubating physician. Some patients had more than one indication for intubation, such as hypersalivation.

Disposition of patients receiving ketamine was as follows; home ($n = 12$, 19%), acute psychiatric services ($n = 15$, 23%), homeless shelter ($n = 2$, 3%), floor admission ($n = 7$, 11%), ICU admission ($n = 28$, 44%). Disposition of patients receiving haloperidol was as follows; home ($n = 43$, 52%), detoxification center ($n = 3$, 4%), acute psychiatric services ($n = 20$, 24%), homeless shelter ($n = 3$, 4%), floor admission ($n = 7$, 9%), ICU admission ($n = 5$, 6%), workhouse ($n = 1$, 1%). For admitted patients, median time in hospital for patients receiving ketamine was 60 hours ($n = 42$, range: 4–894) versus 130 hours ($n = 16$, range: 10–1034) for haloperidol. Physicians more commonly ordered a urine drug screen if the patient received ketamine ($n = 30$) vs. haloperidol ($n = 7$). Results are delineated in Tables 3 and 6. Prehospital (paramedic) diagnoses are recorded in Table 7. Final discharge diagnoses either from the ED or inpatient wards are delineated in Table 8.

Table 4. Complications.

	Ketamine	Haloperidol
Hypersalivation[a]	38% (21/56)	0 (0/69)
Emergence Reaction	10% (5/52)	0 (0/69)
Vomiting	9% (5/57)	3% (2/71)
Dystonia	5% (3/56)	3% (2/69)
Laryngospasm	5% (3/55)	0 (0/69)
Akathisia	2% (1/53)	0 (0/69)
Deaths	0	1% (1/82)

[a]Treatments for hypersalivation: suctioning (4), atropine (6), intubation (11).

Table 5. Primary indications for intubation.

	Ketamine ($n = 25$)	Haloperidol ($n = 3$)
Not Protecting Airway NOS	32% ($n = 8$)	33% ($n = 1$)
Hypersalivation	16% ($n = 4$)	0
Refractory Agitation	12% ($n = 3$)	67% ($n = 2$)
Apnea	12% ($n = 3$)	0
Aspiration/Vomiting	12% ($n = 3$)	0
Laryngospasm	8% ($n = 2$)	0
Seizure	4% ($n = 1$)	0
Traumatic Injuries	4% ($n = 1$)	0

Table 6. Urine drug screen results.

	Ketamine ($n = 30$)	Haloperidol ($n = 7$)
Antidepressants[a]	7	1
Benzodiazepines	4	0
Cocaine	2	1
Diphenhydramine	6	0
Ketamine	28	0
Haloperidol	0	2
Lysergic Acid Diethylamide	1	0
Opioids[b]	2	2
Phenethylamines[c]	10	1
Phencyclidine	0	1
Second Generation Antipsychotics[d]	8	0
Tetrahydrocannabinol	1	0
Negative Screens	1	0

[a]Bupropion [1], citalopram [4 (1 in haloperidol group)], mirtazapine [1], trazodone [1], venlafaxine [1].
[b]Fentanyl [1], hydrocodone [2 in haloperidol group], oxycodone [1].
[c]Amphetamine [1], methamphetamine [7 (1 in haloperidol group)], methylenedioxymethamphetamine [1], methylphenidate [1].
[d]Clozapine [4], olanzapine [2], quetiapine [2].

Table 7. EMS impressions[a].

	Ketamine (n)	Haloperidol (n)
Agitated combative	29	21
Substance abuse	7	23
Behavorial	16	8
Altered mental status	2	10
Traumatic injury or mechanism	4	7
Overdose	0	4
Seizure	0	1

[a]EMS impression unavailable for 14 subjects.

Discussion

Acute undifferentiated agitation in the prehospital environment is both commonly encountered and poorly studied.

Table 8. Final discharge diagnoses.

	Ketamine (*n*)	Haloperidol (*n*)
Patients discharged from ED (total)	29	70
Acute kidney injury	0	1
Agitation	17	13
Altered mental status	16	49
Alcohol intoxication	9	39
Anxiety disorder	1	1
Closed head injury	0	3
Drug intoxication	2	2
Explosive disorder	1	0
Infection	1	2
Laceration	3	6
Overdose	0	2
Psychosis	4	7
Sexual assault	0	2
Suicide attempt	1	3
Suicidal ideation	6	6
Patients discharged from inpatient medical ward (total)	35	12
Accelerated hypertension	2	1
Acute hypoxic respiratory failure		
due to alcohol/trauma	1	1
unspecified	5	0
Acute kidney injury	6	3
Acute toxic encephalopathy		
due to alcohol	8	2
due to PCP	0	1
unspecified	10	4
Agitation/altered mental status	3	3
Alcohol withdrawal	2	1
Anemia	0	2
Electrolyte disturbance	7	4
Frostbite	1	0
High output heart failure	0	1
Hypotension (unspecified)	0	2
Infection	1	1
Lactic acidosis	6	1
Rhabdomyolysis	3	1
Sympathomimetic abuse	5	0
Substance-induced psychosis	1	0
Traumatic injuries	3	1

In this study, ketamine was superior in terms of time to adequate sedation. The median time to adequate sedation of 5 minutes with ketamine is consistent with both procedural sedation literature [8] as well as retrospective data on patients with prehospital acute undifferentiated agitation.[22] Such rapid sedation is ideal to facilitate patient care and facilitates field safety for the patient and paramedics. The median time to adequate sedation of 17 minutes for haloperidol is similar to previous published work both in the prehospital environment [5] and the emergency department.[23] Many EMS systems, including the system in which this study was performed, have transport times similar to or shorter than 17 minutes, calling into question the effectiveness of haloperidol for prehospital acute undifferentiated agitation. Furthermore, in these data, 20% of patients receiving haloperidol required a second sedative injection. The additional risk to prehospital providers of introducing a second needle into a high-risk patient encounter [24] also calls into question the appropriateness of haloperidol as a single agent.

While time to adequate sedation favors ketamine, side effect profile favors haloperidol. Nearly half of patients receiving ketamine experienced some kind of adverse event, some of which were significant. Laryngospasm occurred in 5% of patients receiving ketamine, much higher than the 0.3% rate typically found in patients undergoing procedural sedation.[8] It is also notable that 2 of the 3 patients that experienced laryngospasm required intubation, which stands in contradistinction to the typical course of ketamine-associated laryngospasm where oxygen and bag-valve-mask ventilation is adequate treatment.[25] Vomiting occurred at a rate of 9% in the ketamine group, similar to previous literature.[26] The occurrence of akathisia and dystonia in patients who received ketamine is unexpected given ketamine's mechanism of action, however it is possible these were unrecognized emergence reactions or patients in a partially dissociated state. Emergence reactions occurred in 10% of patients receiving ketamine, also similar to previous literature.[21]

The 39% rate of intubation for patients who received ketamine in these data is quite high. This is particularly surprising as this study included only patients with a lesser degree of agitation (AMSS = +2 and +3) than is typically described in the prehospital ketamine literature where the vast majority of patients would score +4 on the AMSS. In fact, the intubation rate observed in the present study is high even compared to patients with more profound agitation, up to and including patients with excited delirium syndrome. For reference, excited delirium syndrome patients would all score +4 on the AMSS. In a retrospective case series of 49 patients reported by Burnett et al receiving IM ketamine 5 mg/kg for prehospital agitation, they observed a 29% intubation rate.[27] The majority of patients in this case series were diagnosed with the confounder of alcohol intoxication, and the indication for intubation was most commonly noted as "failure to protect airway." Contrary to Burnett et al,[27] we did not observe a positive association between higher doses of ketamine and intubation. This lack of association is consistent with previously published procedural sedation literature [9] as well as a larger retrospective study more recently published.[18] Further study is needed to determine if a link exists between higher doses of ketamine and intubation. Keseg et al. observed a similar intubation rate of 22% in a similar retrospective case series of 36 patients, the vast majority of patients received IM ketamine 4 mg/kg.[28] In contrast to the Burnett and Keseg data, Scheppke et al. observed a very low intubation rate of 4% in a retrospective series of 52 patients receiving 4 mg/kg of IM ketamine for prehospital agitation.[11] In this series only 2 patients were intubated, and the authors thought these intubations were related to co-administered midazolam. However, this data is limited to prehospital records, is not prospective, and does not comment upon ED course for these patients.

The intubation rate of 39% in the present study is notable, as the comparison group receiving haloperidol was intubated only 4% of the time. As noted in the work by Burnett, et al, indication for intubation is often quite vague in this patient population.[23] In the present study, "not protecting airway NOS" was the most common indication for intubation. It may be, in fact, that the receiving emergency physicians were either uncomfortable with a dissociated patient, or may have misapplied the often quoted axiom of "intubation for a Glasgow Coma Scale (GCS) of 8.[29] "A patient dissociated from ketamine most certainly cannot be evaluated properly by the GCS, as they would appear to have a GCS of 3. In this context, it may be better described as "GCS 3K" to denote the influence of the dissociative anesthetic on the scoring.

Nonetheless, this raises the question of whether patients are being intubated simply for a perceived GCS of 3. While this is certainly possible, the side effect profile seen in these data suggests otherwise. For instance, 3 of 64 patients (4.7%) given ketamine were found to have apnea. While the procedural sedation literature suggests apnea occurs with a recommended dose of IM ketamine at 4–5 mg/kg, at a rate closer to 0.8% [7] and is often transient, our observed rate was much higher with two apneic patients requiring intubation. While the etiology of this is unclear, this may be a reflection of co-intoxication, most commonly with ethanol. The synergistic effects of concomitant exposure to multiple sedative-hypnotic medications causing CNS depression is well described in both toxicology [30] and procedural sedation literature.[31] While specific data on an interaction of ketamine and ethanol is lacking, it is conceivable the presence of ethanol in the setting of ketamine administration may prolong the typically brief course of ketamine-related apnea. The same rationale could apply to other CNS depressants, which based on available urine drug screens (Table 6) was very common in this patient population.

Limitations

The primary limitations of the present study are its lack of randomization and blinding. There is some evidence that paramedics were less likely to sedate this patient population when the only available sedative was ketamine as enrollment was lower during this period. This may have introduced bias in that only sicker, more agitated patients received ketamine during that portion of the study. This may have been partially mitigated by the inclusion criteria of a standardized agitation score, however paramedics may have been willing to tolerate the patient's agitation during the ketamine arm whereas they may have administered sedatives during the haloperidol arm. Furthermore, a lack of blinding may have resulted in additional testing in the ketamine arm. For instance, urine drug screens were ordered much more frequently in the ketamine group. No conclusions can be drawn regarding rates of intoxication on stimulants between the two groups because sampling occurred at a much higher rate in the ketamine arm. We suspect this is both due to the dissociated state of the patients as well as an institutional electronic medical record order set frequently used on patients who are intubated in the ED.

A lack of randomization could have led to unequal groups, however baseline demographics and vital signs were similar between groups with the exceptions of initial heart rate, systolic blood pressure, and weight. The discrepancies in weight are likely due to sampling error, as many patients did not have a recorded weight. The higher initial heart rates and systolic blood pressure observed in patients who received ketamine were expected given the adrenergic effects of ketamine.[32]

Randomization was not possible in the current design of this study as its introduction would clearly no longer represent minimal risk to the patient and either an Exception From Informed Consent protocol or consent from a LAR would be required. Though our previous work on agitation in the ED revealed only a small fraction of agitated patients are consentable via LAR[15], it was unclear if consent via LAR would be possible in the prehospital environment. As only 6% of patients in the present study had a LAR present at the scene, we believe further work in this area will require Exception From Informed Consent if prehospital agitation is to be studied in a randomized fashion.

The applicability of these data to the proper patient population is also critical. These data in no way apply to patients with excited delirium syndrome, a patient population that is far more ill than those enrolled in the present study. Patients with excited delirium syndrome experience profound agitation leading to metabolic acidosis, hyperthermia and extremely violent behavior that represent an immediate life-threat to both the patient and their caregivers.[33] These patients require rapid sedation to bring their metabolic abnormalities under control, for which ketamine is an ideal agent.[34] Isbister and colleagues recently observed ketamine to be effective in patients with excited delirium syndrome even after more traditional agents, including droperidol and midazolam, had failed.[35] Despite the high intubation rate and side effect profile observed with ketamine in the present study, the risk-benefit ratio of ketamine is still favorable in the critically ill excited delirium syndrome population.

Conclusions

Ketamine was superior to haloperidol in terms of time to adequate sedation for severe prehospital acute undifferentiated agitation in this prospective observational trial. The median time to adequate sedation of 17 minutes for haloperidol suggests its use as monotherapy is a poor choice for EMS systems with short transport times or where the need for fairly rapid behavior control is indicated. Ketamine, however, is associated with significantly higher complication and intubation rates. These data suggest that using ketamine for prehospital agitation needs to be balanced against the context of risk vs. benefit. Lastly, the absence of legally authorized representatives to provide consent suggests informed consent is not feasible when studying this patient population.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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COMPLICATIONS OF ENDOTRACHEAL INTUBATION AND OTHER AIRWAY MANAGEMENT PROCEDURES

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Introduction

Airway management is a fundamental aspect of anaesthetic practice and of emergency and critical care medicine. Endotracheal intubation (ETI) is a rapid, simple, safe and non surgical technique that achieves all the goals of airway management, namely, maintains airway patency, protects the lungs from aspiration and permits leak free ventilation during mechanical ventilation, and remains the gold standard procedure for airway management. There are also several alternatives to ETI, both for elective airway management as well as for emergency airway management when ETI is difficult or has failed. These devices include the laryngeal mask airway and the combitube. Both ETI and the use of the other airways are associated with complications, some of them life threatening. It is essential for anaesthesiologists to be aware of these complications, and to have an effective strategy to prevent and manage these complications when they arise. A large number of complications have been described. It is beyond the scope of this article to deal with each in detail; emphasis will be laid on the major, potentially life threatening and preventable complications.

Complications associated with ETI

Predisposing factors for complications[1]

The incidence and occurrence may depend on several factors. These include:

Patient factors

1. Complications are likely in infants, children and adult women, as they have a relatively small larynx and trachea and are more prone to airway oedema.
2. Patients who have a difficult airway are more prone to injury as well as hypoxic events.
3. Patients with a variety of congenital as well as chronic acquired disease may experience either difficult intubation or may be more prone to physical or physiological trauma during intubation.
4. Complications are more likely during emergency situations.

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EXHIBIT
tabbies
3

Anaesthesia related factors

The anaesthesiologists:

1. The knowledge, technical skills and crisis management capabilities of the anaesthesiologists play a vital role in the occurrence and outcome of complications during airway management.
2. A hurried intubation, without adequate evaluation of the airway or preparation of the patient or the equipment is more likely to cause damage.

Equipment

1. The shape of the standard endotracheal tube (ETT) results in maximal pressure being exerted on the posterior aspect of the larynx. The degree of damage to these areas depends on the size of the tube and the duration of intubation.
2. Use of stylets and bougies predispose to trauma.
3. Additives to plastic may provoke tissue irritation.
4. Sterilization of plastic tubes with ethylene oxide may lead to production of toxic ethylene glycol if adequate time for drying has not been allowed.
5. Cuff related injuries might occur with the use of high pressure cuffs or inappropriate use of low pressure cuffs.

Complications that may be associated with ETI[2] are listed in Table 1. Flemming classifies hazards of ETI as those that require immediate recognition and management, those related to tissue erosion and healing, and those of lesser significance such as minor trauma.[1]

I. Complications requiring immediate recognition and management

Failed intubation

The difficult airway and failed intubation encompass a spectrum including difficult mask ventilation, difficult laryngoscopy, difficult intubation and failed intubation. The most dreaded situation is a cannot-ventilate-cannot-

Table - 1 : Complicaion of ETI[2]	
At the time of intubation	While the ETT is in place
Failed intubation	Tension pneumothorax
Spinal cord and vertebral column injury	Pulmonary aspiration
Occlusion of central artery of the retina and blindness	Airway obstruction
Corneal abrasion	Disconnection and dislodgement
Trauma to lips, teeth, tongue and nose	Tracheal tube fire
Noxious autonomic reflexes	Unsatisfactory seal
Hypertension, tachycardia, bradycardia and arrhythmia	Leaky circuits
Raised intracranial and intraocular tension	Swallowed ETT
Laryngospasm	
Bronchospasm	
Laryngeal trauma	
Cord avulsions, fractures and dislocation of arytenoids	
Airway perforation	
Nasal, retropharyngeal, pharyngeal, uvular, laryngeal, tracheal, oesophageal and bronchial trauma	
Oesophageal intubation	
Bronchial intubation	

During extubation	After intubation
Difficult extubation	Sore throat
Cuff related problems	Laryngeal oedema
ETT sutured to trachea or bronchus	Hoarseness
Laryngeal oedema	Nerve injury
Aspiration of oral or gastric contents	Superficial laryngeal ulcers
	Laryngeal granuloma
	Glottic and subglottic granulation tissue
	Laryngeal synechiae
	Vocal cord paralysis and aspiration
	Laryngotracheal membrane
	Tracheal stenosis
	Tracheomalacia
	Tracheo-oesophageal fistula
	Tracheo-innominate fistula

intubate (CVCI) situation in an apnoeic anaesthetized patient.[3,4] This is a brain and life threatening emergency occurring in about 1in 10,000 anaesthetics. Failure to achieve oxygenation will result in death or hypoxic brain damage. Repeated attempts at intubation result in more morbidity, and the number of attempts should be restricted to three.[5] In an analysis of 1541 claims,[6] there were 522 (34%) adverse respiratory events. Death or brain damage occurred in 85% of these cases. The main problems were inadequate ventilation (38%), substandard care (90%), oesophageal intubation (18%) and failure to identify problem (48%). The approach to a difficult airway and the management of the difficult airway as well as failed intubation has been outlined in the ASA difficult airway algorithm.[3,4] It is beyond the scope of this article to discuss the algorithm in detail. Methods of emergency ventilation in a CVCI situation include use of the laryngeal mask, combitube or transtracheal jet ventilation. Cricothyrotomy (not tracheostomy) is the preferred method of surgical access to the airway in an emergency such as a CVCI problem. Complications associated with the laryngeal mask and combitube are detailed in a later section. The major problem with jet ventilation is the risk of barotrauma due to pressure of the oxygen jet.[7,8] The risk increases if the airway is obstructed. The ventilatory rate should be restricted to the minimum required to prevent life threatening hypoxia (4-6/min) and a cricothyrotomy or tracheostomy undertaken without delay. A second 20G cannula can be inserted to vent the expired gases.

Oesophageal intubation

Prompt recognition of oesophageal intubation is vital to prevent hypoxia in the apnoeic patient. It may be recognized by gurgling sounds over the epigastrium on auscultation, abdominal distension and absence of breath sounds on the thorax. However all such clinical tests are flawed, and precious lives and brains have been lost by relying on clinical signs of oesophageal intubation. The only certain method of confirming correct placement of the ETT is to visualise its passage though the vocal cords; unfortunately this is not possible during a difficult intubation, a common situation in which oesophageal intubation occurs. End tidal CO_2 monitoring is essential to confirm tracheal placement of the ETT. Passage of a fibreoptic bronchoscope through the ETT and visualization of the tracheal rings and carina also confirms tracheal placement, but is not universally available. Hypoxemia occurring soon after ETI may be due to unrecognised oesophageal intubation. Every attempt should be made to confirm correct placement. There may sometimes be difficulty in deciding whether the tube has been correctly placed; if there is any doubt, the tube should be withdrawn and reintroduced. The old maxim “when in doubt, take it out” still holds true.

Bronchial intubation

Endobronchial intubation occurs if too long a tube is used and inserted into one of the mainstem bronchi. Endobronchial intubation is most common when the distance for the tube tip to be placed properly above the carina yet

below the vocal cords is minimal, as in small children. Standard formulae for the correct length of the ET tube to be inserted may serve as useful guidelines. The unintubated lung does not contribute to gas exchange, and the large volume of blood flowing through this lung results in a substantial right to left shunt resulting in hypoxia. In addition, the intubated lung is hyperinflated, receiving the entire tidal volume, predisposing to overdistension and barotrauma. Signs are those of arterial hypoxaemia, including cyanosis and laboured breathing. In addition, uptake of the inhalation anaesthetic agent may be impaired, resulting in an unexpectedly light plane of anaesthesia. When endobronchial intubation is discovered, the ETT should be withdrawn several centimetres and the lungs inflated to expand atelectatic areas. Fiberoptic bronchoscopy is the optimal diagnostic tool. The clinician must be extremely careful when withdrawing the tube in awkward positions or in the difficult airway. Note also that properly placed tubes may change their position during head movement or repositioning of the patient.[9]

Spinal cord and vertebral column injury

Extension of the cervical spine during laryngoscopy may cause trauma to the spinal cord resulting in quadriplegia. This is more likely in patients with cervical spine fractures or malformations, tumours or osteoporosis. In patients with suspected instability of the cervical vertebrae, the head must be maintained in a neutral position during laryngoscopy and intubation at all times; hyperextension is strictly avoided. The head may be stabilised by in-line manual stabilisation by an assistant. Alternative techniques of airway management that do not involve neck manipulation, such as fibreoptic intubation may be considered.

Noxious autonomic reflexes

Hypertension, tachycardia, arrhythmias, intracranial and intraocular hypertension

Laryngoscopy and ETI produce reflex sympathetic stimulation and are associated with raised levels of plasma catecholamines, hypertension, tachycardia, myocardial ischemia, depression of myocardial contractility, ventricular arrhythmias and intracranial hypertension.[10] Hypoxia and hypercarbia aggravate the autonomic response. The magnitude of the pressor response is related to the duration of laryngoscopy, and may be severe during a difficult intubation with multiple, prolonged attempts at laryngoscopy and intubation. These responses may be particularly deleterious in patients with hypertension, IHD, myocardial dysfunction and raised intraocular and intracranial pressure. In patients with limited coronary or myocardial reserve, myocardial ischemia or failure may follow. The patient with limited intracranial compliance or an intracranial vascular anomaly may suffer serious intracranial hypertension or haemorrhage.

These responses, which also occur during tracheal extubation and suction, can be minimized by rapid, smooth ETI with adequate topical anaesthesia, analgesia, sedation and perhaps the use of muscle relaxants to prevent coughing and bucking during the procedure.

Drugs that tend to block the response to airway instrumentation may be used to blunt these noxious reflex responses. These include fentanyl 3 to 4 $mgkg^{-1}$, alfentanil, lignocaine 1.5 $mgkg^{-1}$ i.v, a small dose of beta antagonist, sublingual nifedipine or intravenous nitroglycerine

Bronchospasm

The presence of an ETT in the trachea produces reflex bronchoconstriction.[11] Bronchospasm may be especially severe in the lightly anaesthetized patient with reactive airways. Bronchospasm may be blunted by the prior administration of anticholinergics, steroids, inhaled b_2-agonists, lignocaine (topical, nerve block, intravenous), and narcotics. After intubation, deepening anaesthesia with intravenous or inhaled agents and the administration of inhaled or intravenous b-agonists are helpful. It is important to ensure that the audible wheezing is not due to mechanical obstruction of the tube or other causes, such as tension pneumothorax, or heart failure.

Drying of mucosa and effects on mucociliary function

The ETT bypasses the humidifying mechanisms in the nose and upper trachea. Inadequate humidification leads to drying of secretions, depressed ciliary motility and impaired mucous clearance. The ETT also provides a surface for pathogenic organisms from the gastrointestinal tract and oropharynx to adhere to and provides direct access for these organisms into the respiratory tract.[12]

Laryngospasm

This may result from attempted intubation of the trachea under light anaesthesia. This can result in hypoventilation, inability to ventilate the lungs and hypoxia, and must be corrected by rapidly deepening the plane of anaesthesia or by giving a muscle relaxant.

Acute traumatic complications

Injury to the lips, teeth, tongue, nose, pharynx, larynx, trachea and bronchi can occur during laryngoscopy and intubation. Traumatic complications have been extensively described in two excellent reviews.[13,14] Most traumatic complications do not result in major morbidity or mortality. However, some require immediate recognition and management. In a review of closed 4,460 claims,[15] airway injuries accounted for 6%. The most frequent sites of injury were larynx (33%), pharynx (19%), and oesophagus (18%). Tracheal and oesophageal injuries were more frequent with difficult intubation. Difficult intubation, age

older than 60 yr and female gender were associated with claims for pharyngo-oesophageal perforation.

Oesophageal, tracheal and bronchial perforation

Oesophageal perforation can occur with attempts at intubation, especially in patients with a difficult airway or multiple attempts. Subcutaneous emphysema may be noticed soon after intubation. Later, neck pain, difficulty in swallowing, neck erythema, and oedema may occur. Mediastinitis leading to sepsis may result in death or serious morbidity. Placement of a nasogastric tube has also been associated with oesophageal perforation.

Tracheal laceration may occur due to overinflation of the ETT cuff, multiple intubation attempts, use of stylets, malpositioning of the tube tip, tube repositioning without cuff deflation, inadequate tube size, vigorous coughing, and nitrous oxide in the cuff. The risk is also greater in patients with tracheal distortion caused by neoplasm or large lymph nodes, weakness in the membranous trachea (seen in women or the elderly), chronic obstructive lung disease, and corticosteroid therapy.

Endobronchial injury can occur with instrumentation of the bronchi. Endotracheal tube guides or tube changers have been associated with endobronchial rupture.[16] Placement of double-lumen ETTs has also been associated with tracheobronchial rupture.[17]

Airway perforation may occur anywhere from the nose to the trachea. It may admit air into unusual locations and manifest as subcutaneous emphysema, pneumomediastinum and pneumothorax. When these occur, a search must be made for such perforations, including by bronchoscopy. Nitrous oxide should be discontinued when pneumothorax or pneumomediastinum is suspected. In awake patients, cough, hemoptysis and cyanosis may occur.

Tension pneumothorax

This can lead to severe hypoxia and hypotension, and can occur after airway perforation during intubation or due to barotrauma during IPPV. It must be suspected either when there is unexplained hypoxia and hypotension, or when they occur with any of the signs of airway perforation. Airway pressure is increased, ventilation of the lungs may be difficult, breath sounds are absent on the affected side with a mediastinal shift to the opposite side, there is a hyper resonant note on percussion, and breath sounds are diminished or absent. An urgent X-ray chest confirms the diagnosis, but in the presence of cardiorespiratory compromise, the pneumothorax must be urgently decompressed by inserting a wide bore cannula in the 2nd interspace on the affected side.

Disconnection and dislodgement

Accidental dislodgment of the ETT during anaesthesia is a potentially lethal complication. Extension of the neck may cause cephalad movement of the ETT tube. Poor or loose fixation of the tube, excessive movement of the head during surgery, inadequate access to the tube during head and neck surgery or neurosurgery and heavy connectors producing drag on the circuit and ETT may lead to dislodgement. It can be detected rapidly if airway pressure and capnography are being continuously monitored. In the intensive care unit, the longer a tube stays in-situ, the greater the chances of kinking, blockade and unplanned extubation, leading to hypoventilation and hypoxia. Unplanned extubations have reported an incidence ranging from 0.3–30 %.[18,19] Inadequate sedation, agitation, inadequate nursing supervision and inadequate fixation of the ETT predispose to accidental extubations in the ICU.[20]

Failure to achieve satisfactory seal

Inadequate cuff seal is a common problem, leading to hypoventilation during Mechanical Ventilation (MV) and aspiration of gastric contents. The common causes of leak during MV and their solutions are outlined in Table-2. More serious causes[21] include tracheomalacia and tracheo-oesophageal fistula [TEF]. Inflation of the cuff leads to weakening of tracheal cartilage and widening of the trachea. Progressively increasing volumes of air are then required to maintain cuff seal.

Table - 2 : Common problems leading to leak during mechanical ventilation.[21]

Problem	Solution
Eccentric cuff inflation	Check cuff before insertion
Incorrect cuff position, cuff at or above vocal cords	Check and adjust ETT position, ensure cuff is in mid-trachea
Size of ETT is too small	Change ETT, insert a larger ETT
Leak in inflation valve	Attach 3-way stopcock and keep closed to maintain seal
Leak in pilot balloon or valve	Cut the connecting tube distal to leaking part housing and insert 22G needle with 3-way stopcock into remaining tubing
Leaking cuff, usually damaged by teeth, nasal bone or Magill forceps	Change ETT

Obstruction of the tube[2,9]

This can be due to a number of reasons :

1. Biting of the ETT.
2. Kinking of the ETT.
3. Obstruction by material in the lumen of the tube. This includes inspissated secretions, blood clots, nasal turbinates, adenoids or a variety of foreign bodies.

4. Defective spiral embedded tubes. During manufacture, air bubbles may form between layers. Blebs form when these are steam sterilized with vacuum. Diffusion of nitrous oxide into these blebs causes dissection of the walls with compression of the lumen.
5. Impaction of the tip of the tube against the tracheal wall may result in respiratory obstruction, particularly where the trachea contains a sharp bend, such as the thoracic inlet. The Murphy's eye, incorporated into many modern tubes, permits airflow to take place, even if this has occurred.
6. Herniation of the cuff over the lumen of the tube may occur if the cuff of an old, perished tube is over inflated. This, again, will cause respiratory obstruction.
7. Compression of the lumen of the tube by the cuff may be caused by over inflation of the cuff or by gradual diffusion of nitrous oxide onto the cuff during the course of anaesthesia. This problem is more common when silicone rubber tubes are used.

Obstruction of the ETT may manifest as increased resistance to ventilation, high airway pressures and 'wheeze'. A blocked tube is an important cause of intraoperative bronchospasm and must be ruled out before bronchodilator therapy is given. ETT obstruction may be prevented by careful attention to the type of ETT, inspection and checking of the ETT and cuff prior to use, and by humidification of inspired gases. When ETT obstruction is diagnosed, visual inspection, passage of a suction catheter (or preferably a fiberoptic bronchoscope) along with cuff deflation and 90^0 rotation of the tube will rule out several of these possibilities. If patency cannot be restored, the ETT should be removed and replaced, if necessary over a tube exchanger.

Aspiration of gastric contents

While a cuffed tube protects the lungs from aspiration of foreign material, aspiration does occur. The high volume low pressure cuff has folds even after inflation through which fluid can pass into the trachea and lungs. The presence of spontaneous ventilation, accumulation of fluid above the cuff, a head up position and the use of uncuffed tubes or cuff leakage increase the chances of aspiration.

Fire during laser surgery[9]

Fires are a danger associated with the increasing use of lasers for airway and oral surgery. Steps that may be taken to reduce this extremely serious hazard include:

1. Using special laser tubes, which may be made of jointed metal or clear plastic (with no radiopaque strip), or a plain red rubber tube, but not a conventional plastic tube.
2. Wrapping exposed portions of the tube with aluminium tape.
3. Inflating the cuff of the ETT with saline instead of air.
4. Packing wet pledgets between the ETT and larynx and covering the external part of the ETT with wet drapes.
5. Use of helium-oxygen mixtures that are less supportive of combustion than oxygen alone or oxygen-nitrous oxide mixtures.

When a fire in the airway occurs, the flow of oxygen must be immediately stopped, saline poured on the ETT and the trachea extubated. Surgery is stopped, the trachea is reintubated and the patient given humidified oxygen. The airway should be examined for burn injury and for any missing fragments of the ETT or its wrapping.

Difficult extubation[10]

1. The cuff may fail to deflate. It can be punctured by a needle placed through the cricothyroid membrane after the cuff is raised to this level.
2. More serious and somewhat unusual causes of difficult extubation include fixation of the ETT or pilot tube by a Kirshner (K) wire used in head and neck surgery or a suture placed from the pulmonary artery through the trachea into the ETT. The nature of the surgical procedure must be kept in mind when a tube will not come out after cuff deflation or rupture, so as to avoid trauma from vigorous extubation attempts. Direct or fiberoptic examination may be required.

Complications of extubation[10]

Airway obstruction, laryngospasm, and aspiration can occur. After intubations lasting 8 hours or more, airway protection may be impaired for 4 to 8 hours.

Sore throat is a complication of anaesthesia that may have pharyngeal, laryngeal, and/or tracheal sources and may occur in the absence of ETI. Factors that may affect the incidence of sore throat include area of cuff trachea contact, use of lignocaine ointment and size of the ETT, and the use of succinylcholine. Cuffs with a longer cuff trachea interface appear to cause a higher incidence of sore throat. The incidence of sore throat may also be related to intracuff pressures. The mechanism for succinylcholine-related sore throat is postulated to be myalgias due to fasciculations of peripharyngeal muscles. Sore throat is a minor side effect that should resolve within 72 hours; it should not be a factor in determining whether ETI is required.

Hoarseness is another minor side effect correlated with ETT size that should be investigated if persistent.

Laryngeal oedema[10]

Subglottic oedema is particularly more common in children, as the nonexpandable cricoid cartilage is the narrowest part of the pediatric airway. Oedema may also be uvular, supraglottic, retroarytenoid, or at the level of the vocal cords, and is manifested by inspiratory stridor. Diminished stridor may represent total airway obstruction and movement of air must be repeatedly confirmed. The contributing factors to the production of laryngeal oedema include too large a tube, trauma from laryngoscopy and/or intubation, excessive neck manipulation during intubation and surgery, excessive coughing or bucking on the tube, and present or recent upper respiratory infection. The prophylactic use of steroids before extubation to reduce oedema is an unproven but frequently utilized treatment if the likelihood of postextubation stridor is suspected. Treatment includes warmed, humidified oxygen, nebulized racemic epinephrine (0.25 to 1 ml), and I.V. dexamethasone (0.5 $mgkg^{-1}$ up to 10 mg). If obstruction is severe and persistent, reintubation must be considered.

Acute traumatic complications of lesser significance[13,14]

Dental injury

Incidence of dental injury ranges from 1:150 to 1:1000, to as little as 1:9000.[22] The upper incisors are usually involved. Risk factors include preexisting poor dentition and one or more indicators of difficult laryngoscopy and intubation.[23] When dental trauma occurs, the loose tooth should be recovered to ensure that aspiration of the tooth does not occur. The avulsed tooth should be placed in saline and immediate dental consultation should be obtained for possible reimplantation. A partial or complete dental fracture should be evaluated by an oral surgeon postoperatively. Details of the injury should be well documented in the anaesthetic record and chart and the patient informed of the injury.

Nasal injury

Nasotracheal intubation is frequently used in head and neck surgery. Patients with basilar skull fractures or severe facial trauma should not have nasal tubes passed as there exists a danger of inadvertent cranial intubation.

Epistaxis is a common problem, caused by the tip of the ETT traumatizing nasal and pharyngeal mucosa. This may be more common and dangerous in patients with coagulopathy or those receiving anticoagulants. Nasal intubation is relatively contraindicated in such patients.

Attempted passage of a nasotracheal tube can create false submucosal passages. These can progress to retropharyngeal abscesses.

Turbinates, adenoids, and tonsils can also be traumatized. Prolonged nasal intubation can lead to pressure necrosis of the nostrils and septum. Nasal septal abscesses, retropharyngeal abscesses and paranasal sinusitis can occur after intubation. Paranasal sinusitis[24] occurs due to injury to the sinus ostia followed by oedema, obstruction and infection. It may present as unexplained fever or purulent discharge, is often refractory to antibiotics and may lead to intracranial infection or septicaemia.[25]

Pharyngeal trauma

Necrosis and perforation of the pharynx may present in the immediate postoperative period with subcutaneous crepitus, fever, tachycardia, and odynophagia. Most lacerations of the oropharynx can be treated conservatively. A haematoma should be treated with antibiotics, but if it is large, consideration should be given to drainage. The patient must avoid oral feeds for at least 48 hours and intravenous broad-spectrum antibiotics should be prescribed. Larger perforations may need surgical repair.

Temporomandibular joint injury

Patients tend to be healthy females below 60 years of age. Preexisting temporomandibular disease may be present in a small percentage. The dislocation usually is detected at the time of procedure and the jaw is locked in an open position and cannot be closed. Immediate reduction of the dislocated TMJ should be performed and this can be achieved easily. Patients with continual symptoms referable to the joint should receive an oral surgery consultation for possible treatment with an occlusal appliance.

Tongue injury

Macroglossia occurs due to prolonged compression by an ETT or oral airway, leading to ischemia and venous congestion. Obstruction of the submandibular duct by an ETT may lead to massive tongue swelling.[26] Compression injury to the lingual nerve during difficult intubation leading to loss of sensation has been reported.

Laryngeal trauma

Vocal cord paralysis

In the subglottic larynx, an anterior branch of the recurrent laryngeal nerve enters between the cricoid and the thyroid cartilage, innervating the intrinsic muscles of the larynx. An inflated cuff at this location can compress the nerve between the cuff and the overlying thyroid cartilage, causing injury.[27,28] Bilateral injuries present considerably more risk and frequently require emergency reintubation or tracheostomy. Unilateral injury to a

recurrent laryngeal nerve prevents abduction of the ipsilateral vocal cord; therefore, it becomes fixed in the adducted position. This is associated with hoarseness, usually noted immediately in the postoperative period. Recurrent nerve injury can be prevented by avoidance of overinflation of the ETT cuff, and prevention of excessive tube migration during anaesthesia. Vocal cord paralysis is usually associated with spontaneous recovery over days to months.

Arytenoid injury

Arytenoid dislocation is another well described cause of laryngeal injury that can occur after traumatic intubation[29] as well as with routine elective intubation.[30]

II. Complications related to tissue erosion and healing

Laryngeal injury : Occurs due to ischemic injury resulting from high pressures generated [upto 400 mmHg] when the round ETT presses on the pentagonal structure of the larynx, especially at the vocal processes of the arytenoids and the cricoid ring.[31]

Ulcerations or erosions of the larynx : Are common even after a short duration of intubation, and progress with the length of intubation. They are most commonly found on the posterior part of the larynx and anterior and lateral aspects of trachea, corresponding to the position of the convex curve of the ETT, the tip and the cuff. Superficial ulcers heal rapidly. Deeper ulcers may result in scarring or erosion of a blood vessel and haemorrhage.

Granuloma of the vocal cords : May develop from an ulcer, when granulation tissue forms and forms a sessile lesion. The incidence varies from 1: 800 to 1: 20000. Patients may be asymptomatic, or have hoarseness, pain and discomfort in the throat, chronic cough and haemoptysis. Persistent symptoms after intubation need an ENT consult and strict voice rest. Granulomas usually heal spontaneously. Surgical intervention is required only if the lesion is pedunculated or the patients develops respiratory obstruction.

Laryngotracheal membrane : Is an uncommon but potentially fatal complication due to respiratory obstruction. The symptoms of respiratory obstruction occur 24-72 hours after extubation. Diagnosis is made by direct laryngoscopy or bronchoscopy. Treatment is removal by suction.

Delayed tracheal injury : Is almost always cuff related, and can be minimized by use of low pressure cuffs and meticulous cuff management. The incidence of laryngotracheal complications can be further reduced by use of appropriate sized ETTs made of nontoxic plastic. Drag on the ETT by ventilator tubing should be avoided and excessive ETT movement reduced by use of swivel connectors. Local and systemic sepsis should be aggressively treated and corticosteroids used only when indicated.

Tracheal stenosis : Intracuff pressure is transmitted laterally against the wall of the trachea. Ischemia and eventual necrosis occur when the lateral tracheal wall pressure exceeds the capillary perfusion pressure of about 25 mmHg. Necrosis of the tracheal mucosa leads to sloughing and ulceration of the mucosal membrane, exposing tracheal cartilage. Continued ischemia may be followed by partial or complete destruction of cartilaginous tracheal rings and loss of the structural integrity of the affected tracheal segment, leading to tracheal dilatation. Healing of the injured tracheal segment during any stage of this process may lead to a tight fibrous stricture (tracheal stenosis). These can be prevented by proper management of low pressure cuffs. Only high volume, low pressure cuffs must be used, and the cuff inflated to pressure not exceeding 25 mmHg or 30 cm H_2O. Overinflation of these cuffs causes them to function just like high pressure cuffs. It is therefore essential to inflate only as much air as is required to just seal the air leak during IPPV (minimal inflation technique), and to check the intracuff pressure with a cuff-pressure manometer.

Complications of tracheostomy

Two types of tracheostomy (TR) are now performed – open or surgical tracheostomy, and percutaneous tracheostomy. The complications of TR[32-34] are summarized in Table 3. Some of these are:

Table - 3 : Complications of tracheostomy	
A.	Complications during surgery
	Haemorrhage
	Pneumothorax and pneumomediastinum
	Cardiorespiratory arrest
	Recurrent laryngeal nerve injury
B.	Immediate postoperative complications
	Haemorrhage
	Subcutaneous emphysema
	Displacement and obstruction of the tube
	Swallowing problems
C.	Late complications
	Tracheal stenosis: at the stoma or at the level of the cuff
	Tracheomalacia
	Tracheo-oesophageal fistula
	Tracheo-innominate fistula

1. Pneumothorax : Occurs in about 4% of adult TRs and is more common during emergency or difficult TR, especially when the airway is obstructed and the patient's inspiratory efforts draw in a large volume of air into tissue planes. False passage of the tracheostomy tube (TT) in the anterior paratracheal tissue followed by mechanical ventilation (MV) leads to similar complications. Tension pneumothorax may lead to cardiac arrest. A chest X ray must be taken after TR and if pneumothorax is present, it should be promptly treated by drainage and underwater seal. Subcutaneous emphysema can be prevented by using a cuffed TT and by not suturing the wound very tightly.

2. Cardiorespiratory arrest : The respiratory drive and massive sympathetic stimulation occurring due to hypercarbia and hypoxia in patients with severe airway obstruction are suddenly removed when TR is performed, leading to respiratory arrest and cardiovascular collapse. The patient usually recovers completely with MV, fluid resuscitation and inotropic support. Negative pressure pulmonary oedema[36] may also occur minutes to hours after airway obstruction is relieved by TR [or ETI]. It responds well to treatment.

3. Inability to insert the TT : Can result in severe hypoxia and death. During TR, the ETT should never be withdrawn completely from the larynx until it is confirmed that the TT is in the trachea. The TR tract takes 37 days to form. If in this period, the TT needs to be reinserted, there is a real danger of being unable to reinsert the tube or of inserting it into the paratracheal space. A pad must be placed under the shoulders to bring the trachea up in the neck and a tracheal dilator used to introduce the TT. ETI may be necessary to secure the airway if the TT cannot be replaced. A Bjork flap [an inverted 'U' shaped flap of anterior tracheal wall cut and sutured to the skin] may permit easier reinsertion of the TT before the tract has formed, but may be associated with a higher incidence of stomal stenosis.

4. Trachea stenosis and tracheomalacia : Can be prevented by proper management of low pressure cuffs. The incidence of stomal stenosis can be reduced by not making a large stoma and by use of lightweight, mobile, swivel connectors to minimize mechanical trauma.

5. Tracheo-oesophageal fistula : May occur due to injury to the posterior tracheal wall during TR, but is more often the result of high cuff pressures, and is often aided by a nasogastric tube pinched between the oesophagus and posterior tracheal wall.

6. Tracheo-innominate fistula[37] : Is a dreaded complication of TR, the patient exsanguinating to death in minutes. It is a major cause of haemorrhage occurring 48 hours after TR and occurs either due to direct contact between the innominate artery and TT in case of low TR [below the 4 th tracheal ring] or to high cuff pressures leading to necrosis of the anterior tracheal wall followed by erosion of the arterial wall. Major haemorrhage may be preceded by 'warning bleeds' and the TT may be seen to be pulsating. Haemorrhage may be controlled by hyperinflating the cuff to occlude the opening in the artery. If this is unsuccessful, the artery can be compressed anteriorly after incising the skin over the sternal notch while the patient is transported to the operating room. Immediate surgery is required to salvage the patient.

Complications of percutaneous tracheostomy

The incidence of complications reported with PCT varies from 3-25%, In three large series using the Ciaglia technique, perioperative complications were reported in 8-11% of patients.[38-40] The published incidence of perioperative complications with the guidewire dilating forceps (GWDF) technique[41-43] ranges from 0-24%. Fikkers and Ambesh found no major differences between the GWDF and the Blue Rhino techniques,[44,45] except perhaps for a slightly increased bleeding with the GWDF.[45] In a meta analysis of percutaneous tracheostomy trials (n=27; patients) 1817 perioperative complications occurred in 10%, including deaths in 0.44% and serious cardiorespiratory events in 0.44% patients, whereas postoperative complications occurred in 7% of patients.[46] The main perioperative complications of PCT include bleeding, pneumothorax, and posterior tracheal injury. Posterior tracheal injury may be confined to the mucosa, or may involve the entire posterior wall, and more seriously, result in a tracheo-oesophageal fistula. It has been suggested that visualization by fibreoptic bronchoscopy of tracheal puncture and dilatation can substantially reduce the incidence of such complications.[47,48] Endoscopic guidance ensures midline placement, prevents paratracheal tube placement and avoids inadvertent injuries. Complications during percutaneous tracheostomy have been classified[46] as major, intermediate and minor (table 4).

Table - 4 : Complications of percutaneous tracheostomy

Major	Intermediate	Minor
Death or cardiac arrest Pneumothorax Post tracheal tear Tracheo-oesophageal fistula Intratracheal haemorrhage Pulmonary aspiration of blood Obstruction or displacement of the tube Sepsis Tracheal stenosis	Hypoxemia Bleeding (requiring surgical intervention, blood transfusion or hemoglobin fall > 2gm%) Posterior tracheal wall injury Conversion to surgical tracheostomy Abandoned procedure	Minor Haemorrhage Subcutaneous emphysema Pretracheal dilatation Puncture of ETT cuff Arterial puncture

Complications with the laryngeal mask airway

The laryngeal mask airway (LMA) has become an increasingly popular alternative to the face mask and ETT as a means of providing a secure airway for patients undergoing elective surgical procedures requiring general anaesthesia. However, the use of LMA is not free of complications. These have been reviewed by Pollack.[49] Complications resulting from use of the LMA in the OR are known to be rare. In a series of more than 11,000 patients of all ages over a 2-year period, there was a 0.15% airway management complication rate, and none of these 18 patients required intensive care.[50]

Malplacement and aspiration

The commonest and the most important are regurgitation of gastric content and chances of aspiration. Brimacombe conducted a meta analysis of the published literature and found an incidence of aspiration in 2/10,000 patients, which is similar to that recorded during general endotracheal anesthesia.[51] The LMA has been shown to cover both the laryngeal inlet and the oesophagus, thus forming a potential direct communication between the two. Moreover LMA does not reliably provide an airtight seal around the larynx and may not protect the airway from aspiration of gastric contents, if there is regurgitation into pharynx. The chance of regurgitation and aspiration while using LMA is present both during spontaneous and mechanical ventilation. The incidence of regurgitation varies from 0.08 to 23%.[52-53] Mechanical ventilation with an LMA may encourage the risk of reflux and aspiration more, by causing gastric insufflations and increased intragastric pressure.[54] Regurgitation is considered to occur more often during certain surgical procedures, such as laparoscopic surgery in gynaecological patients. This is thought to be due to lithotomy position with head down tilt which increases intra abdominal pressure,[55] there is also the possibility that the LMA induces a reduction of lower oesophageal sphincter tone.[56] Malplacement and improper seating of the LMA above the airway opening clearly increases the risk of gastric distension and subsequent aspiration, as does positive pressure ventilation through the LMA. There are case reports of aspiration even with Proseal LMA.[57]

Inadequate patient anaesthesia may result in coughing, gagging, and bucking on attempted LMA insertion. This may be particularly hazardous in the patient with suspected intracranial or cervical spine injury. If coughing and gagging occur during attempted insertion, the mask should be removed and anaesthesia should be deepened. If they occur with the mask in situ, anaesthesia should be deepened and the mask should be left in place. Direct trauma to pharyngeal and upper airway structures typically may result from poor insertion technique.

Malplacement of the LMA, with migration of the LMA tip into the glottic aperture, may also induce bronchospasm. Ventilation through an LMA in these patients may be inadequate because high positive pressure ventilation results in air leak around the laryngeal mask.

Pressure induced lesions

The next important complication, which has been reported, is lingual nerve injury, both unilateral and bilateral. The course of lingual nerve after it branches out of posterior trunk of mandibular nerve is such that the various manoeuvers undertaken during the insertion of LMA and in maintaining its position can injure it. The nerve is vulnerable to compression as it travels between the pterygoids or between the medial pterygoid and the mandible. Compression injury between the pterygoids may occur secondary to mandibular retraction.[58] Prolonged anterior displacement of the mandible, as in the jaw thrust manoeuver, has also been implicated in lingual neuropraxia. The LMA can also cause nerve injury probably by direct compressions of the nerves. When the laryngeal mask is correctly placed, the distal tip lies in the hypopharynx at the upper oesophageal sphincter, the proximal base lies just under the tongue base with sides facing the pyriform fossa.[59] In this position the cuff may compress the lingual nerves as they lie on the inner aspect of the mandible covered only by the mucus membrane.[60]

Tongue cyanosis and swelling has also been reported after the use LMA.[61] The probable cause may be occlusion of lingual artery bilaterally by the cuff of LMA when the arteries enter the base of tongue. It may be due to malpositioning or due to size of LMA.

The incidence of recurrent nerve paralysis has also occurred by the use of LMA. The probable cause may be the compression of the nerve by increased cuff pressure of the LMA at the point where the nerve enters into the larynx passing behind the thyroid and cricoid cartilage.

Cuff volume also influences postoperative sore throat and dysphagia. The incidence of sore throat has

also been found to be higher in case of LMA than that of ETT. It has been found that sore throat incidence is less with Soft-Seal LMA than classic LMA.[62] Nitrous oxide tends to diffuse less into the Soft Seal cuff during anaesthesia.

Complications of using the esophageal tracheal combitube (ETC)

The combitube has been widely accepted as an airway device for out-of hospital Cardio pulmonary and cerebral recuritation (CPCR) but has not been accepted into routine anaesthesia practice. The main limitation of the ETC in routine anaesthesia is the potential risk of trauma.

Oesophageal and pharyngeal perforation leading to subcutaneous emphysema, pneumomediastinum and pneumoperitoneum has been reported in association with out of hospital airway rescue.[63,64] Bleeding (36-45%), sore throat (16-46%) and dysphagia (8-68%) have been reported in association with routine anaesthesia.[65,66] Possible mechanisms for trauma are direct injury during placement or high pressures exerted against the surrounding mucosa.

The chances of direct injury during the placement of ETC are due to the following reasons:

1. ETC is a large and stiff tube with an anterior curvature, a design that might cause injuries by bulging the anterior wall of oesophagus. Laceration has been observed on the anterior wall only.
2. Technique of blind insertion with out visualization of the passage of the ETC into the pharynx and into the proximal oesophagus opening may also promote injuries.

The volume of both the proximal and the distal cuffs determines the pharyngeal, oesophageal and tracheal mucosal pressures. Pharyngeal mucosal perfusion is progressively reduced when mucosal pressure increases from 34 to 80 cmH_2O.[67] In the pharynx and in the oesophagus the pressure will be highest posteriorly because the posterior surface is adjacent to the rigid vertebral bodies.[68] In the pharynx the ETC can potentially impair the perfusion in the anterior, lateral and posterior wall when the proximal cuff volume increases from 40 to 70 ml, 50 to 80ml, and 30 to 50 ml respectively.[68] These volume frequently exceed the minimal volume required to form an oropharyngeal leak pressure of 30 cm H_2O.

In the oesophagus perfusion would be potentially impaired in the anterior, lateral and posterior oesophagus when distal cuff volume increases from 12 to 18 ml, 12 to 20 ml and 4 to 8 ml respectively. Likewise tracheal mucosal perfusion is progressively reduced when mucosal pressure increases from 30 to 50 cmH_2O. Tracheal perfusion would be potentially impaired in the anterior, lateral and posterior trachea, when distal cuff volume increases from 4 to 6 ml, 8 to 10 ml and 10 to 12 ml, respectively. Thus at the recommended inflation volume for the pharyngeal (85 ml) and oesophageal cuffs (10-15 ml), mucosal pressure would be potentially higher than perfusion pressure posteriorly.[68]

In the pharynx, the increased pressure may cause bleeding and sore throat and would perhaps predispose to pharyngeal perforation. Likewise, in the oesophagus these high pressures may cause dysphagia and may predispose to oesophageal rupture.

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Original Contribution

A prospective study of ketamine as primary therapy for prehospital profound agitation

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ABSTRACT

Objective: We investigated the effectiveness of ketamine as a primary therapy for prehospital profound agitation.
Methods: This was a prospective observational study of patients receiving 5 mg/kg of intramuscular ketamine for profound agitation, defined as a score of +4 on the Altered Mental Status Scale (AMSS), a validated ordinal scale of agitation from −4 (unresponsive) to +4 (most agitated). The primary outcome was time to adequate sedation (AMSS < +1). Secondary outcomes included need for additional sedatives, intubation frequency, complications associated with ketamine, and mortality.
Results: Forty-nine patients were enrolled. Median age was 29 years (range 18–66); 76% (37/49) were male. Median time to adequate sedation was 4.2 min (95% CI: 2.5–5.9, range 1–25 min) and 90% (44/49) had adequate sedation prehospital. Seven patients (14%) received a second sedative prehospital. Intubation occurred in 57% (28/49) of patients. Mechanical ventilation lasted <24 h in 82% (23/28) of patients, and <48 h in 96% (27/28) of patients. A single physician intubated 36% (10/28) of the patients. Complications related to ketamine included hypersalivation (n = 9, 18%), vomiting (n = 3, 6%), and emergence reaction (n = 2, 4%). One patient died from complications of septic shock on hospital day 29, likely unrelated to ketamine.
Conclusions: In patients with prehospital profound agitation, ketamine provides rapid effective sedation when used as a primary therapy. Intubation was common but accompanied by a short duration of mechanical ventilation and appears to have been subject to individual physician practice variation.
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1. Introduction

1.1. Background

Agitation is a common problem for prehospital providers [1]. Agitation exists on a spectrum from those patients who respond to verbal de-escalation techniques [2] to profound agitation requiring immediate sedation for the safety of the patient and their caregivers [3]. Profound agitation may culminate in excited delirium syndrome (ExDS), a condition associated with significant morbidity and mortality where patients experience metabolic acidosis and hyperadrenergic autonomic dysfunction that may result in death [4,5].

Profound agitation, including ExDS, is best managed with rapid chemical sedation to decrease endogenous heat and acid production and to facilitate additional evaluation and care [6]. Though the optimal drug for parenteral chemical sedation of agitated patients in the prehospital environment is not yet known, multiple options have been proposed including droperidol [7], haloperidol [7,8], and benzodiazepines such as midazolam [8,9]. Recently the use of ketamine for agitation in the prehospital environment has gained favor [3,10-12].

We recently completed a trial of ketamine versus haloperidol for severe agitation. In that trial we used the Altered Mental Status Scale (AMSS), a validated [13,14], ordinal scale of agitation from −4 (unresponsive) to +4 (combative, most agitated possible) to define severe agitation as an AMSS score of +2 or +3, and profound agitation as an AMSS score of +4 [15]. That prior study included only patients with an AMSS score of +2 or +3, and demonstrated that ketamine effectively sedated patients with severe agitation (AMSS +2 or +3) typically within 5 min. Patients with profound agitation (AMSS +4) were specifically excluded from that comparative trial for purposes of patient and provider safety. Based on over a decade of experience successfully treating profound agitation with ketamine, our institution at the time deemed it unethical and unsafe to withhold ketamine from these patients for their safety as well as the safety of EMS. Although these profoundly agitated patients were excluded from that trial, prospective data were still collected on them for quality assurance purposes, which we now report in the present study.

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1.2. Importance

Profound agitation may be a precursor to ExDS and its significant metabolic disturbances [16]. Though the final common pathway for death in ExDS is not known, expert consensus suggests it involves a combination of acidosis, hyperthermia, and sympathomimetic surge [4]. Volunteer law enforcement studies on "use of force" encounters demonstrate these conditions, if left unchecked, worsen over time [17]. Therefore, if ketamine can rapidly sedate these patients it may curb or prevent the complications of ExDS. To our knowledge no study has prospectively assessed the effectiveness of ketamine as a primary therapy for profound agitation in the prehospital environment.

1.3. Goals of this investigation

The aim of the current study was to prospectively assess the effectiveness of ketamine 5 mg/kg intramuscular (IM) for profound agitation (AMSS +4) in the prehospital environment, by analyzing data collected on profoundly agitated patients during our comparative trial. Time to adequate sedation was the primary outcome. Secondary outcomes included additional sedatives required prehospital, complications associated with ketamine, intubation frequency, ECG and laboratory data, and hospital length of stay.

2. Methods

2.1. Study design

This was an IRB approved Waiver of Consent [18] observational study of patients receiving ketamine for profound agitation (AMSS +4) within the EMS primary service area subsequently transported to the study hospital's Emergency Department (ED) during our comparative trial on severe agitation (AMSS +2 or +3) [15]. The comparative trial was originally designed as a blinded, randomized trial, and registered at ClincalTrials.gov under identifier number NCT02103881. For feasibility reasons the comparative trial was later redesigned as a before and after open label trial and withdrawn from ClinicalTrials.gov.

2.2. Study setting and population

This study was conducted from October 2014 to November 2015 at an urban Level 1 trauma center safety-net hospital (in conjunction with its hospital-based EMS agency) with >110,000 annual ED visits. Data were collected during the period our comparative trial took place. The participating EMS agency is 1 of 5 agencies within the EMS system. This EMS agency responds to over 75,000 calls annually, serving an urban and suburban population of over 1,000,000 covering >200 mile^2. All ambulances are staffed with two EMT-paramedics at all times. Mean scene time for the agency is 17.9 min; mean transport time is 12.2 min. Approximately 500 patients per year receive chemical sedation for agitation (severe or profound combined) within the EMS agency. The EMS agency regularly transports patients to the study hospital as well as 10 other hospitals; only patients transported to the study hospital were included for analysis.

All paramedics within the EMS agency were trained in the Altered Mental Status Scale (AMSS), a validated [14] agitation scale regularly used in research at our institution [15,19] (Table 1). The AMSS was chosen as an agitation measurement tool not only because of our familiarity with it, but because it was developed on intoxicated, agitated, ED patients [13] and has been used in agitation studies in both the United States [15,19] and Australia [14,20]. Because the AMSS provides information on both the degree of agitation and the depth of sedation, it can be used to determine time to adequate sedation. Training was completed both via an online video and at in-person training sessions led by the primary investigator. All paramedics were required to pass a quiz containing example patients for all nine points on the AMSS; a correct AMSS score needed to be assigned for all nine cases. The study hospital's ED was staffed 24 h a day, 7 days a week, 365 days a year with research associates (RAs) trained in an identical manner in the AMSS. Research associates consisted of undergraduate and medical students reporting to research coordinators. In addition, RAs were proctored by senior RAs for their initial cases, and intermittently took refresher quizzes designed to keep scoring standardized.

Profound agitation was defined by two criteria, both of which were required for enrollment. This first criterion was based upon our EMS agency's standard operating procedure for behavioral emergencies, and is defined as "a patient with active physical violence to himself/herself or others evident, and usual chemical or physical restraints may not be appropriate or safely used." [3] The second criterion for inclusion was an AMSS score of +4. All patients in our EMS agency with profound agitation receiving ketamine who were transported to the study hospital's ED were included, regardless of the etiology of agitation. Exclusion criteria included obviously gravid women and persons who appeared to be or were known to be <18 years of age.

2.3. Study protocol

All patients with profound agitation (AMSS +4) received ketamine dosed at 5 mg/kg IM with dose calculation made by paramedic-estimated weight in the field if the weight was unknown. AMSS scores were recorded by medics on a standard data collection form at time = 0 and every 5 min thereafter until adequate sedation was achieved. Paramedics calculated total time to adequate sedation in minutes (primary outcome) by using a hand held stopwatch. Time to adequate sedation was defined as the time from ketamine administration, until the patient achieved an AMSS score < +1.

Immediately upon ED arrival, paramedics transferred both the stopwatch and data collection form to RAs. In the circumstance where adequate sedation was not reached prehospital, RAs continued recording AMSS scores every 5 min or until adequate sedation was reached.

2.4. Measurements

In addition to time to adequate sedation and AMSS scores, RAs also prospectively assessed, in conjunction with the treating physician, for

Table 1
The Altered Mental Status Scale.

Score	Responsiveness	Speech	Facial expression	Eyes
+4	Combative, very violent, or out of control	Loud outbursts	Agitated	Normal
+3	Very anxious, agitated, mild physical element of violence	Loud outbursts	Agitated	Normal
+2	Anxious, agitated	Loud outbursts	Normal	Normal
+1	Anxious, restless	Normal	Normal	Normal
0	Responds readily to name in normal tone	Normal	Normal	Clear, no ptosis
−1	Lethargic response to name	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (<half eye)
−2	Responds only if name is called loudly	Slurring or prominent slowing	Marked relaxation (slacked jaw)	Glazed and marked ptosis (>half eye)
−3	Responds only after mild prodding	Few recognizable words	Marked relaxation (slacked jaw)	Glazed and marked ptosis (>half eye)
−4	Does not respond to mild prodding or shaking	Few recognizable words	Marked relaxation (slacked jaw)	Glazed and marked ptosis (>half eye)

complications associated with ketamine (hypersalivation, vomiting, emergence phenomena, tachydysrhythmias, laryngospasm), intubation (including indications for intubation), history of mental illness or chemical dependency as recorded in the electronic medical record (Epic, Verona, WI), initial ED vital signs, and laboratory data including serum lactate, venous pH, serum bicarbonate, serum potassium, serum creatinine, serum creatinine kinase (CK), breath and serum ethanol concentrations, QTc duration as measured by computer calculated Bazett's formula, and urine drug screening. Urine drug screens included a battery of 12 immunoassays in addition to liquid and gas chromatography with mass spectrometry capable of screening for over 1000 different compounds, though the vast majority of novel psychoactive substances (such as synthetic cannabinoids and "bath salts") were not detectable.

2.5. Analysis

Descriptive statistics were used to analyze data. Data were collected on Microsoft Excel 2010 (Microsoft, Redmond, WA) and analyzed using STATA (Version 12, StataCorp, College Station, TX).

3. Results

3.1. Characteristics of study subjects

A total of 545 patients received chemical sedation for agitation during the study period. One hundred and forty-six patients with an AMSS of +2 or +3 were enrolled in the comparative trial. Of the remaining patients, 158 were assigned an AMSS score of +4 and received ketamine making them eligible for inclusion. Of these 158 patients, 56 were transported to the study hospital; of these, 7 patients were excluded (1 for age <18, 6 for inactivated stopwatches) leaving 49 patients for final analysis. Enrollment is displayed in Fig. 1. Prehospital data, including paramedic impressions and vital signs before and after ketamine, are described in Table 2. Baseline demographics and vital signs are described in Table 3. Initial laboratory and ECG data are described in Table 4. Though we did not assess for this a priori, 3 of the 49 patients who were enrolled may not have met the traditional definition of profound agitation, but were in fact active "jumpers" threatening or attempting suicide. Two were preparing to jump off bridges; a third had jumped into highway speed traffic but did not suffer severe traumatic injuries. This patient population has been managed with IM ketamine in our EMS agency since 2004 [21].

3.2. Main results

Median time to adequate sedation was 4.2 min (95% confidence interval [CI]: 2.5–5.9, range 1–25 min). Adequate sedation was achieved prehospital in 90% (44/49) of cases. Seven patients (14%) received a second sedative medication prehospital (1 patient received 10 mg of IM midazolam, 6 patients received additional doses of IM ketamine ranging from 100 to 500 mg). Median initial ketamine dose was 4.9 mg/kg (range 2.1–7.5 mg/kg, based upon weights obtained in the ED). Complications included hypersalivation (n = 9, 18%), vomiting (n = 3, 6%), and emergence phenomena (n = 2, 4%). Four patients received atropine for hypersalivation, two of which were intubated. No patient suffered a tachydysrhythmia or laryngospasm. One patient died 29 days into his hospitalization from complications related to septic shock. This patient presented with hypoglycemia, a condition described to mimic or contribute to ExDS [6]. Details of the case are available in Fig. 2. No other fatalities occurred.

Intubation was common and occurred in 57% (28/49) of patients, all in the ED. No patients were intubated prehospital; all 7 patients receiving additional sedation prehospital were intubated. For intubated patients who had a weight recorded in the ED (n = 28), the median ketamine dose was 4.7 mg/kg (range, 2.1–7.5). For patients who were not intubated that also had a weight recorded (n = 18), median ketamine dose was 5.2 mg/kg (range, 3.4–6.8). Primary indications for intubation, determined by the intubating physicians, are listed in table 5. Of the approximately 30 physicians providing attending coverage in the ED during the study period, a single physician who works exclusively night shifts intubated 10/28 (36%) study patients. Emergency Medicine fellows, physicians pursuing subspecialty fellowship training in ultrasound, EMS, or critical care medicine and all in their first year of practice, intubated another 6 patients (21%). One physician intubated 3 patients, another intubated 2 patients, and the remainder of the physicians in the group intubated one or no patients. Duration of mechanical ventilation for all intubated patients is displayed in Fig. 3. Five patients self-extubated in the ICU.

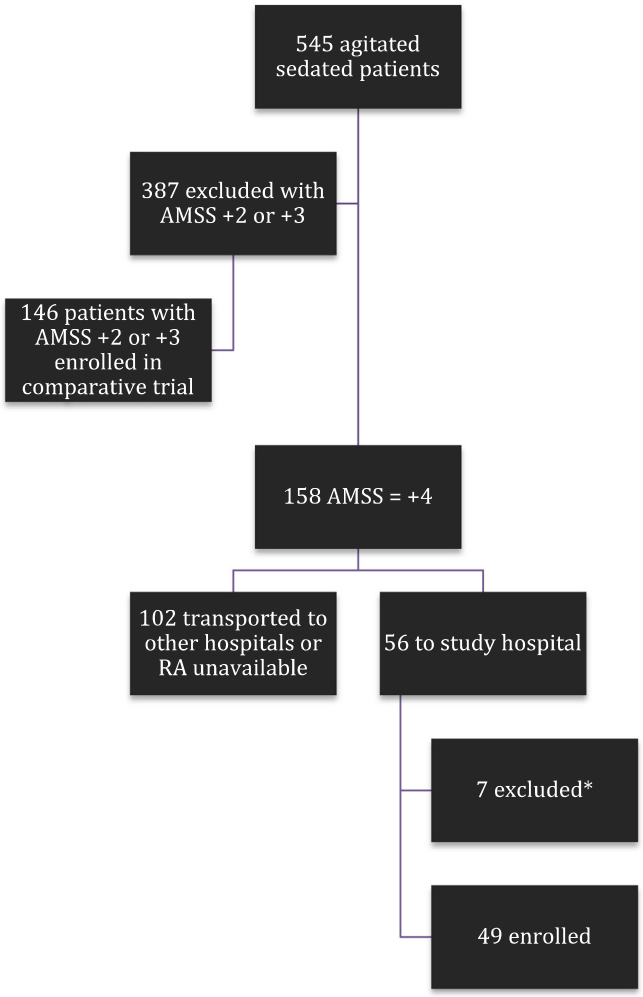

Fig. 1. Study enrollment. *One patient excluded for age < 18, 6 patients excluded for inactivated stopwatches.

Disposition of patients included intensive care (n = 28), acute psychiatric services, (n = 13), home (n = 7), and homeless shelter (n = 1). For admitted patients, median time in hospital was 35 h (range 6–690). For patients discharged from the ED, median ED time was 542 min (range 229–995). Final discharge diagnoses from either the ED or inpatient wards are noted in Table 6.

4. Discussion

Based on the short time to adequate sedation demonstrated in this study, ketamine appears effective for profound agitation in the prehospital environment. Profound agitation is important to recognize and treat aggressively in order to ensure patient and provider safety. Prospective studies evaluating treatment strategies for agitation of any severity in the prehospital environment are sparse. A small study comparing haloperidol and midazolam with only 5 patients in each arm

Table 2
Prehospital data.

Primary EMS impressions	(n)
Agitated combative	23
Behavioral	14
Substance abuse	4
Altered mental status	3
Traumatic injury or mechanism	3
Seizure	2
Vital signs *before* ketamine (n = 12)[a]	Median (range)
Heart rate (beats/min)	115 (64–150) n = 9
Systolic blood pressure (mm Hg)	148 (112–182) n = 7
Respiratory rate (breaths/min)	22 (16–30) n = 9
Pulse oximetry (%)	100 (100) n = 2
Vital signs *after* ketamine (n = 41)[b]	Median (range)
Heart rate (beats/min)	120 (65–176) n = 41
Systolic blood pressure (mm Hg)	166 (120–260) n = 31
Respiratory rate (breaths/min)	16 (12−30) n = 40
Pulse oximetry (%)	98 (74–100) n = 39

[a] One patient had no prehospital vital signs recorded.
[b] Five patients had vital signs recorded both pre and post ketamine.

Table 3
Demographics.

	AMSS = +4, received ketamine (n = 49)
Age (median, years)	29 (range, 18–66)
Gender (n)	
Male	37 (76%)
Female	12 (24%)
Race (n)	
Caucasian	24 (49%)
Black American	17 (35%)
American Indian	3 (6%)
Hispanic	1 (2%)
Somali	1 (2%)
Unknown or mixed	3 (6%)
History of mental illness	
Any mental illness	34 (69%)
Depression	17 (34%)
Generalized anxiety disorder	9 (18%)
Previous suicide attempt	7 (14%)
Bipolar disorder	6 (12%)
PTSD	4 (8%)
ADHD	4 (8%)
Antisocial personality disorder	4 (8%)
Adjustment disorder	3 (6%)
Borderline personality disorder	1 (2%)
Conduct disorder	1 (2%)
Fetal alcohol syndrome	1 (2%)
Learning disability NOS	1 (2%)
Mood disorder NOS	1 (2%)
Personality disorder NOS	1 (2%)
Psychosis NOS	1 (2%)
Schizoaffective disorder	1 (2%)
Schizophrenia	1 (2%)
Traumatic brain injury	1 (2%)
History of chemical dependency	
Polysubstance abuse	9 (18%)
Alcohol abuse	8 (16%)
Chemical dependency NOS	4 (8%)
Cocaine abuse	2 (4%)
Initial ED vital signs	Median (range)
Weight (kg)[a]	86 (61.6–149.7)
Heart rate (beats/min)	118 (54–152)
Systolic blood pressure (mm Hg)	155 (100−201)
Respiratory rate (breaths/min)	18.5 (8–33)
Pulse oximetry (%)	97 (72–100)
Temperature (°C)	36.7 (34.7–39.4)
ED arrival time of day	
Day shift (7 am–3 pm)	10
Number intubated	8 (80%)
Evening shift (3 pm–11 pm)	24
Number intubated	8 (33%)
Night shift (11 pm–7 am)	15
Number intubated	12 (80%)

[a] Weights recorded for only 39 patients.

found the average time to adequate sedation for IM midazolam (maximum dose, 5 mg) for prehospital agitation was 13.5 min, and 25 min for IM haloperidol (maximum dose 5 mg). None of these patients had ExDS [8]. In our recently completed comparative trial, we found the median time to adequate sedation for 10 mg of IM haloperidol was 17 min, though none of these patients had an AMSS score of +4 or ExDS. Benzodiazepines, most commonly midazolam, are often recommended for ExDS, though time to adequate sedation may be problematic. A larger study of midazolam for agitation in the ED, given as an initial 15 mg IM dose, found that even at 20 min 11% of patients had not yet reached adequate sedation [22].

The median time to adequate sedation of 4.2 min observed in the present study of profoundly agitated patients (AMSS +4), with 90% of patients achieving adequate sedation prehospital, was quite similar to our findings in the ketamine arm of our comparative trial on severe agitation (AMSS = +2 or +3) where the median time to adequate sedation for the same dose of ketamine was 5 min [15]. This suggests a 5 mg/kg dose of IM ketamine should provide rapid sedation regardless of the patients' degree of agitation.

ExDS is an important clinical subset of profound agitation, characterized by acidosis and hyperadrenergic autonomic dysfunction, typically in the setting of acute on chronic drug abuse, serious mental illness, or a combination of the two [4]. Recognition and treatment of ExDS is essential, as this syndrome is associated with significant morbidity and mortality. No prior clinical trials have compared sedative agents in ExDS, but expert recommendations suggest using midazolam or ketamine [4]. While midazolam is theoretically attractive in ExDS as many ExDS patients are intoxicated on sympathomimetics, there is concern midazolam may be too slow to adequately sedate the patient in a timely manner and may also contribute to respiratory depression, thus worsening acidosis. The success of ketamine in achieving rapid sedation in this profoundly agitated cohort, some of whom likely had ExDS, suggests ketamine is a promising treatment in this population.

Intubation was extremely common in the present study with 57% of patients intubated in the ED. Studies on the use of ketamine for prehospital agitation that include ED data report intubation rates of 23% [12], 29% [23], 38% [15], and 63% [24]. As agitation is a vaguely defined disorder and can result from myriad conditions including psychiatric illness, trauma, metabolic disturbances, sepsis, or drugs of abuse, it is expected rates of intubation would vary from study to study. Previous work at our institution revealed intubation after prehospital ketamine for profound agitation was associated with male gender and ED arrival between 11 pm and 7 am, but not higher ketamine doses, additional sedatives administered, or concomitant intoxication on ethanol or sympathomimetics [24]. This analysis also demonstrated tremendous individual practice variation; of the 10 attending physicians in our ED encountering at least 5 profoundly agitated patients treated with prehospital ketamine, intubation rates ranged from 0 to 100% (median = 60%, IQR = 25–92%) [24].

It is noteworthy that with the present data included, the three studies on prehospital use of ketamine for agitation with the highest intubation rates all originate from our institution [15,24]. While it is possible that these cohorts have been more ill than others due to chance, it is likely this represents either a local practice variation or specific physician practice variation. For instance, examination of the practice of the

Table 4
Presenting ED laboratory and ECG data.

	Median (range)
Serum lactate (mmol/L)	3.0 (1.2–>14.8) n = 42
Venous pH	7.33 (6.91–7.49) n = 39
Venous pCO_2	42 (27–60) n = 38
Serum bicarbonate (mmol/L)	22 (6–30) n = 48
Anion gap	12 (2−31) n = 48
Serum potassium (mmol/L)	3.8 (2.9–5.9) n = 48
Serum creatinine (mg/dL)	1.03 (0.57–7.05) n = 48
Serum total CK (IU/L)	342 (52–4699) n = 18
Breath ethanol (mg/dL)[a]	194 (78–363) n = 17
Serum ethanol (mg/dL)[a]	161 (47–316) n = 39
QTc interval[b]	409.5 (271–468) n = 47
Urine drug screen results (n = 33)	
Negative screens	3 (9%)
Amphetamines[c]	4 (12%)
Antidepressants[d]	3 (9%)
Antipsychotics[e]	5 (15%)
Benzodiazepines	6 (18%)
Caffeine	3 (9%)
Cocaine	4 (12%)
Cocaine metabolite (benzoylecgonine)	6 (18%)
Diphenhydramine	4 (12%)
Ketamine	25 (76%)
Ketamine metabolite (norketamine)	8 (24%)
Opioids[f]	7 (21%)
Other drugs[g]	4
Phencyclidine	1 (3%)

[a] Reported median of detectable concentrations. Among those with undetectable ethanol concentrations: (breath, n = 5), (serum, n = 22).
[b] Computer calculation using Bazett's formula.
[c] Amphetamine [1], methamphetamine [3].
[d] Citalopram [2], venlafaxine [1].
[e] Haloperidol [3], quetiapine [1], risperidone metabolite [1].
[f] Fentanyl [2], oxycodone [2], buprenorphine & metabolite [1], hydrocodone [1], methadone [1].
[g] Cyclobenzaprine [1], hydroxyzine [1], levamisole [1], phenytoin [1].

Table 5
Primary indications for intubation (n = 28).

Airway unprotected NOS	36% (n = 10)
Hypersalivation	18% (n = 5)
Respiratory failure NOS	14% (n = 4)
Hemodynamic instability/acidosis	11% (n = 3)
Failure to treat agitation	7% (n = 2)
"Expected return of anticipated behavior"	7% (n = 2)
Status epilepticus	3.5% (n = 1)
Hypoxia	3.5% (n = 1)

physician in the present study responsible for 36% (10/28) of all intubations is enlightening. Previous analysis of 135 patients receiving prehospital ketamine for profound agitation at our institution found this physician, along with one other, (both of whom work almost exclusively night shifts) were responsible for 51% (28/55) of night encounters, but 65% (27/41) of overnight intubations [24]. These same two physicians saw 7.5% (6/80) of patients receiving ketamine on the day shift but were responsible for 11.4% (5/44) daytime intubations [24]. Though we have not previously observed intubation to be associated with ketamine dosing, other authors have posited lower doses may be associated with fewer intubations [23]. Prospective, comparative data are needed to assess the effect of ketamine dose on intubation, and to assess the relative risks and benefits of higher doses.

In addition, the indications for intubation in the present study also suggest some of the intubations may have been unnecessary. The most common intubation indication was "Airway Unprotected NOS." This vague indication for intubation suggests there may be other factors in the decision to intubate the patient. Improper use of other clinical scores such as the Glasgow Coma Scale (GCS) may have played a role; for instance, it is possible the often quoted axiom of "intubate for a GCS of 8" was misapplied in some cases [25], as a patient dissociated on ketamine would appear to have a GCS of 3, or perhaps more accurately, "GCS 3K" to denote the dissociative effect of ketamine on the score [15]. Misapplication of a GCS score to a patient dissociated on ketamine may have been used to justify inappropriate intubations.

Hypersalivation was the second most common indication for intubation, yet only 2 of 5 patients intubated for hypersalivation received atropine. The fact that intubation was used as primary therapy for hypersalivation over a trial of an anticholinergic drug coupled with suction suggests some of these intubations may have been unnecessary as well. Examination of the 3 "jumper" cases is also revealing. Two of these three patients were intubated; both were cared for by the physician responsible for 36% of intubations. These two patients had normal laboratory studies (with the exception of ethanol intoxication) and were rapidly extubated in the ICU; one 4 h later, the other 6 h later. It is likely these patients were unnecessarily intubated. Last, 18% of intubated patients in the present study were cared for by Emergency Medicine fellows, all in their first year of practice. The sum of shifts worked by fellows in our ED is similar to the number of shifts worked

Paramedics were called to the home of a 66-year-old 157 kg insulin-dependent diabetic man who had recently been ill; he had seen his primary physician the day before who had recommended hospital admission. On arrival the patient was agitated and uncooperative. His initial vital signs were as follows: pulse 120 beats/min, blood pressure 182/100, respiratory rate 26 breaths/min, pulse oximetry 100% on room air, point-of-care glucose, 45 mg/dL. He became progressively agitated and violent; 15 minutes of verbal de-escalation attempts failed. Multiple firefighters and police officers were at the scene but because of the patient's size and degree of violent behavior they believed physical restraint was unsafe. Online medic control was contacted; at the physician's direction 500 mg of IM ketamine was administered. In the emergency department the patient was found to be in acute renal failure (serum creatinine 7.8 mg/dL) and septic shock from a urinary tract infection (culture positive for *Enterobacter cloacae*). He also had bilateral pneumonia. His blood gas revealed uncompensated respiratory and metabolic acidosis; he was subsequently intubated. He had persistent encephalopathy after resolution of his infectious and metabolic conditions attributed to his prolonged hypoglycemia which resulted from his septic shock and impaired insulin clearance in the setting of acute renal failure. He died on hospital day 29 after care was withdrawn.

Fig. 2. Case narrative of the single fatality.

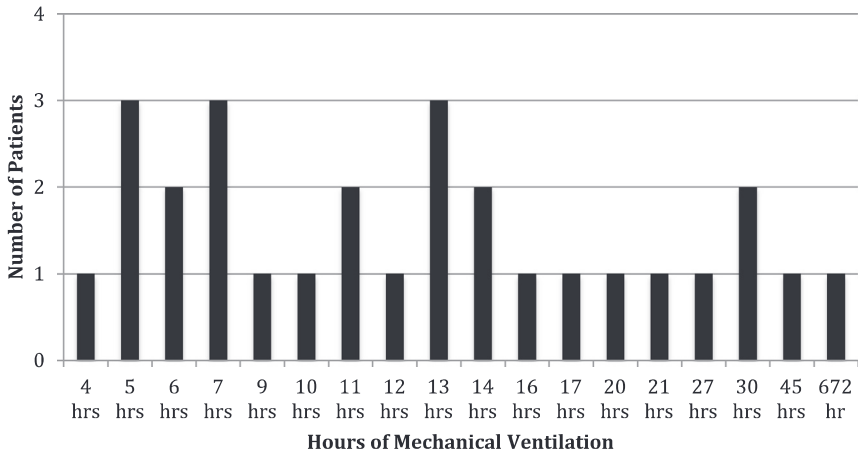

Fig. 3. Bar graph displaying duration of mechanical ventilation for intubated patients (n = 28).* *The single fatality in the study was the patient intubated for 672 h.

Table 6
Final discharge diagnoses.

	(n)
Patients discharged from ED (total)	21
Agitation	14
Altered mental status	14
Alcohol intoxication	9
Amphetamine intoxication	1
Hallucinations	1
Huffing	1
Hypokalemia	1
Laceration	2
Lactic acidosis	1
Mood disorder	2
Psychosis	2
Rhabdomyolysis	1
Suicide attempt	4
Suicidal ideation	3
Tooth subluxation	1
Patients discharged from inpatient medical ward (total)	28
Acute hypoxic respiratory failure	1
Acute kidney injury	6
Acute toxic encephalopathy	21
Due to alcohol	10
Due to cocaine	5
Due to "gravel"/"flakka"	1
Due to methamphetamine	3
Due to phencyclidine	1
Due to synthetic cannabinoids	1
Agitation	4
Anticholinergic delirium	1
Aspiration pneumonia	2
Encephalopathy NOS[a]	1
Heart failure	1
Hepatic encephalopathy	1
Hypernatremia	1
Hyperpyrexia	1
Hypertensive crisis	1
Hypoglycemia[a]	1
Hypothermia	1
Lactic acidosis	7
Mood disorder	2
Psychosis	1
Rhabdomyolysis	3
Seizures	3
Septic shock[a]	1
Stab wound of face	1
Status epilepticus	1
Transaminitis	1
Traumatic brain injury	1

[a] The single fatality.

by one full-time faculty physician; thus when taken as one "whole physician" our ED fellows were the second most likely to intubate. The experience of the receiving emergency physician may be related to the decision to intubate a patient who arrives dissociated. Targeted education for both paramedics and physicians about ketamine's effect on GCS as well as pharmacotherapy for hypersalivation before the study may have curbed the intubation rate. EMS agencies and receiving hospitals looking to adopt a similar protocol may benefit from such education prior to initiating a similar ketamine protocol. Regular quality reviews of patients who are intubated may also ensure intubation for these patients is performed in a judicious manner.

Some authors have argued that intubation following ketamine for agitation should be classified as an adverse event [26]. Complications may arise from the intubation itself, such as tube malpositioning, aspiration, hypoxia, and pneumothorax [27]. Intubation is associated with longer hospital stays [28], and mechanical ventilation itself may have complications, including ventilator-associated pneumonia (VAP) and tracheal stenosis. The duration of mechanical ventilation, however, plays an important role in complications. Tracheal stenosis is most commonly a complication of prolonged ventilation [29], and VAP, by definition, requires mechanical ventilation for >48 h [30]. In 23 of 28 of our intubated cases (82%), the duration of mechanical ventilation was <24 h. Of the remaining 5 patients 4 were extubated within 48 h. As the duration of mechanical ventilation in our study was short, it is likely the intubation itself and not the subsequent mechanical ventilation that is most likely to represent risk to the patient. The rate of difficult intubation in this patient population has not been established; as such minimizing unnecessary intubations should be a priority. When intubation does occur, post-intubation monitoring is critical; 5 patients in our study self-extubated, consistent with previous literature demonstrating agitation is a risk factor for self-extubation [31].

While some patients with profound agitation clinically require intubation either to control agitation refractory to multiple sedative doses or facilitate a medical work-up, the general goal of the emergency physician should be to avoid intubation in a patient with a protected airway. While not all intubations for agitation should be regarded as untoward outcomes, in our study it is likely a considerable, though indeterminate, number of intubations were indeed adverse events. Even when intubation occurs without complications, the inappropriate use of mechanical ventilation represents a potential risk for the emergency department as a whole. Reduced ICU bed availability is associated with a decreased likelihood of admission [32], and delays in ICU disposition from the ED are associated with adverse outcomes [33]. If inappropriately intubated

patients are occupying ICU beds, adverse outcomes may occur in the other critically ill patients simultaneously in the ED.

4.1. Limitations

This study has several important limitations. First, as this is a prospective observational study, no formal comparison with any other agent is possible. Certainly there are advocates for both antipsychotics, such as droperidol [34], as well as benzodiazepines, most commonly midazolam [35]. Previous work suggests midazolam, droperidol and haloperidol would all have a longer onset time compared to ketamine, though no comparative studies exist for profound (AMSS +4) agitation in the prehospital environment.

Second, this study may be limited by its patient selection. As this study is a subgroup of excluded patients from a larger trial, it is subject to inherent selection bias. Adherence to inclusion criteria may not have been strict. While all paramedics in the agency completed AMSS training, AMSS scores of +4 may have been assigned incorrectly. The 3 "jumper" cases are worth scrutinizing as an example. While these three patients met the descriptive definition of profound agitation ("active physical violence to him or herself") they likely did not meet the intended definition of AMSS +4 as they were not actively combative or out of control in a traditional sense. It is possible patients such as these biased the laboratory and drug screen results making the cohort appear less agitated overall. Furthermore the fact that these less agitated patients were included among the AMSS +4 patients may have biased our results to favor ketamine; it is possible ketamine may have been less effective if only truly actively combative patients were included. This effect may have been exacerbated further by the fact that the majority of eligible AMSS +4 patients were transported to other hospitals and thus excluded from final analysis.

Third, this study was conducted partially during an outbreak of synthetic cannabinoid abuse which was associated with significant morbidity and mortality [36]. Though we have a robust toxicology laboratory the vast majority of novel psychoactive substances were not detectable by our lab. This may have biased the results of our urine drug screens to make the prevalence of acute drug intoxication, and perhaps ExDS, appear lower than it actually was.

Fourth, paramedics and RAs were unblinded to the treatment medication. Paramedics may have been biased towards ketamine's effectiveness and assigned lower agitation scores to declare adequate sedation sooner. This significant limitation may be addressed by future blinded, randomized studies.

Fifth, while there appears to be significant benefit to rapid sedation of patients with ExDS, the assumption cannot be made that all patients in this study had ExDS. A patient with an AMSS score of +4 will have some features of ExDS, but the heterogeneity of our subjects' final diagnoses (Table 6) suggests that while some of our patients may have had ExDS, some did not. Previous retrospective work using a very similar agitation scale (−4 to +4) has equated a score of +4 with ExDS [16], but the lack of standardized criteria for ExDS [37] makes prospectively identifying patients extremely difficult. Nevertheless, control of profoundly agitated patients, even without ExDS, is still important as it facilitates rapid diagnosis and may prevent ExDS from developing.

Sixth, complications were assessed for based upon clinical definitions and experience. While this is not problematic for vomiting or tachydysrhythmias, apnea, emergence phenomenon, and laryngospasm may have been less accurately diagnosed. For example, emergence phenomenon was diagnosed clinically by the treating physician; it is possible the physicians were merely witnessing the unmasking of the underlying agitation as ketamine's effect waned.

Last, the high intubation rate makes assessing for complications such as vomiting, emergence phenomenon, and apnea difficult. Our comparative trial on less agitated patients suggested rates of all three of these complications occurred more frequently. If physicians chose to immediately intubate the patient on arrival due to their personal practice pattern, there may not have been time for these complications to develop. Individual practice variation, including the relative inexperience of Emergency Medicine fellows, also limits the generalizability of our findings to other systems. Larger, prospective, multi-center studies including prehospital and hospital data would address this limitation.

4.2. Conclusions

In summary, ketamine administered at 5 mg/kg IM provided rapid sedation (median time to adequate sedation 4.2 min) to patients with profound agitation (AMSS +4) in the prehospital environment. Intubation was common but was accompanied by a short duration of mechanical ventilation and appears to have been subject to individual physician practice variation. These data highlight the need for prospective, comparative data to assess both the effectiveness and optimal dose of ketamine compared to other sedatives for the profoundly agitated patient in the prehospital environment.

Conflicts of interests/declarations

None.

Prior presentations

A version of this project was presented as an oral presentation at the 2016 Society for Academic Emergency Medicine (abstract #59).

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Successful Management of Excited Delirium Syndrome with Prehospital Ketamine: Two Case Examples

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CASE CONFERENCE

SUCCESSFUL MANAGEMENT OF EXCITED DELIRIUM SYNDROME WITH PREHOSPITAL KETAMINE: TWO CASE EXAMPLES

Jeffrey D. Ho, MD, Stephen W. Smith, MD, Paul C. Nystrom, MD, Donald M. Dawes, MD, Benjamin S. Orozco, MD, Jon B. Cole, MD, William G. Heegaard, MD, MPH

ABSTRACT

Excited delirium syndrome (ExDS) is a medical emergency usually presenting first in the prehospital environment. Untreated ExDS is associated with a high mortality rate and is gaining recognition within organized medicine as an emerging public safety problem. It is highly associated with male gender, middle age, chronic illicit stimulant abuse, and mental illness. Management of ExDS often begins in the field when first responders, law enforcement personnel, and emergency medical services (EMS) personnel respond to requests from witnesses who observe subjects exhibiting bizarre, agitated behavior. Although appropriate prehospital management of subjects with ExDS is still under study, there is increasing awareness of the danger of untreated ExDS, and the danger associated with the need for subject restraint, whether physical or chemical. We describe two ExDS patients who were successfully chemically restrained with ketamine in the prehospital environment, and who had good outcomes without complication. These are among the first case reports in the literature of ExDS survival without complication using this novel prehospital sedation management protocol. This strategy bears further study and surveillance by the prehospital care community for evaluation of side effects and unintended complications. **Key words:** excited delirium; agitation; ketamine; prehospital; chemical restraint

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INTRODUCTION

Excited delirium syndrome (ExDS) is a medical emergency characterized by the clinical constellation of profound psychomotor agitation and delirium. As a semantic term, ExDS was first coined in the mid-1980s by Wetli and Fishbain to describe a series of deaths in Florida that were preceded by this clinical behavior.[1] At the time, it was felt to be a behavioral manifestation due to acute cocaine intoxication. Since that time, other writings have connected this syndrome to other illicit intoxicants as well as underlying mental illness.[2,3]

The concept of ExDS is generally defined as a spectrum of clinical behaviors and signs that includes aggressive behavior with an altered sensorium, hyperthermia, exhibition of "superhuman" strength, diaphoresis, and lack of willingness to yield to overwhelming force.[4] Severe ExDS is associated with a high mortality rate and has emerged as a significant public safety problem. The pathophysiology leading to death in ExDS is postulated to be profound metabolic acidosis and unchecked catecholamine surge.[4] This has led some prehospital systems to develop protocols for treatment of suspected ExDS with the goal of interrupting the downward spiral of worsening pathophysiology.[5]

We describe two cases of successful ExDS management without complication utilizing ketamine as a chemical restraint in the prehospital environment. We believe that these cases are among the first description in the medical literature of this novel management strategy describing overall success with no complications. This strategy bears further study and surveillance by the prehospital care community for evaluation of side effects and unintended complications.

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CASE REPORTS

Case 1

In January 2012, a 35-year-old, 103-kilogram white man was exhibiting bizarre behavior in an urban alley. He was observed to be shirtless (the environmental temperature was 11°F/–11.7°C) and trying to enter a business that was not open. When confronted by a security officer, he exhibited agitation, vocal perseveration, partial nudity, and incoherence. As the security officer tried to detain him, he became more agitated and violent, prompting a call to 9-1-1 for help. Although this was not known at the time of the 9-1-1 call, he was later noted to have a history of multiple psychiatric and polysubstance abuse problems.

Two law enforcement officers (LEOs) arrived and attempted to control the subject, but were unsuccessful. They later described their attempts as futile and noted that the subject was remarkably strong and did not react to manual pain compliance-control techniques. They requested help, and multiple LEOs responded to assist until there were a total of eight LEOs on the scene struggling with the subject. Emergency medical services (EMS) arrived and described the subject as prone on the ground, with each of the eight LEOs attempting to restrain an extremity, the head, or the buttocks, but instead being easily tossed around despite their advantageous numbers, training, equipment, and positioning. They described the subject as forcefully striking his own head on the pavement while yelling nonsensically. Two LEOs were injured during this process. The LEOs used only manual control techniques (no impact, aerosolized, or conducted-electrical weapons) during their attempts and reported that these techniques were ineffective.

The subject was eventually brought under control with a 500-mg intramuscular (IM) injection of ketamine hydrochloride in the buttocks administered through clothing. The total time from security guard encounter to sedation was reported to be less than 12 minutes. The EMS providers reported excellent sedation within 4 minutes after the ketamine administration. Prehospital vital signs included a pulse rate of 122 beats/min and a respiratory rate of 32 breaths/min. The EMS personnel reported that a full set of vital signs was not obtained because of the combativeness of the subject. He was immediately transported to a nearby tertiary receiving hospital in handcuff restraints in a semiprone/recovery position.

Upon arrival at the hospital emergency department (ED), he was noted to be sedate and unresponsive to verbal or painful stimuli, with the following vital signs: temperature 102.4°F/39.1°C, pulse rate 122 beats/min, respiratory rate 32 breaths/min, blood pressure 128/58 mmHg, and oxygen saturation 100% on room air. He was kept in four-point restraints on arrival as a precaution. The primary survey was notable for rapid, deep, and labored breathing.

Analysis of the subject's blood for standard resuscitation biomarkers was performed on arrival. The following were of interest in this case: arterial pH 7.00, partial pressure of carbon dioxide (pCO_2) 54 mmHg, and bicarbonate 13 mEq/L; venous potassium 3.4 mEq/L, creatinine 1.9 mg/dL, troponin I qualitatively "normal" (no further testing done), and creatine kinase (CK) 2,562 units/L; urine drug screen was positive for metabolites of cocaine but did not indicate acute cocaine usage. An initial lactate level was not obtained, but when analyzed three hours after admission the level was 0.9 mg/dL.

The patient was endotracheally intubated and placed on a mechanical ventilator because of concern for his significant acidosis. The results of a computed tomographic head scan and a lumbar puncture were both normal. The patient was admitted to the intensive care unit and over the course of the next 72 hours was weaned off of sedation and extubated. With the exception of CK level, which peaked at 3,402 units/L at 48 hours after admission, the patient's serum abnormalities quickly returned to normal. His mental status returned to normal and his psychiatric status was verified to be at baseline by hospital day 3. He did not remember his violent behavior and was amnestic to the restraint and sedation event. He admitted to chronic cocaine abuse but denied recent, acute use surrounding this event. He was discharged from the hospital and lost to follow up after 96 hours with the diagnoses of altered mental status with agitation and combativeness, acidosis, rhabdomyolysis, acute kidney injury, and fever.

Case 2

In February 2012, a 40-year-old, 80-kilogram African American man was involved in a violent altercation with a woman. Her screams during the assault prompted bystanders to call 9-1-1. Although this was not known at the time of the 9-1-1 call, the subject was later shown to have a history of schizophrenia with paranoid features, chronic cocaine abuse, chronic alcohol abuse, and hepatitis B. Upon the arrival of LEOs, it was noted that the subject was uncooperative, agitated, partially nude (the environmental temperature was 17°F/–8.3°C), and incoherent. He was noted to be screaming numerous requests to speak with God. A request for an EMS response to be present was made at that time. A significant fight with the LEOs ensued, including a brief foot chase for no more than one city block. The subject was eventually brought under control with deployment of a single conducted-electrical weapon (TASER X26 device, TASER International, Inc., Scottsdale, AZ) and then was tackled by several LEOs. EMS was present and chemically sedated him with

375 mg of IM ketamine hydrochloride in the thigh. The time from LEO encounter to sedation was reported to be less than 8 minutes. EMS reported good effect from the sedative in approximately 3 minutes. Prehospital vital signs included a pulse rate of 123 beats/min and a respiratory rate of 42 breaths/min. EMS reported that a full set of vital signs was not obtained because of the combativeness of the subject. He was immediately transported to a nearby tertiary receiving hospital in handcuff restraints in a semiprone/recovery position.

Upon arrival at the ED, he was noted to be sedate and unresponsive to verbal or painful stimuli, with the following vital signs: temperature 101.3°F/38.5°C, pulse rate 168 beats/min, respiratory rate 35 breaths/min, blood pressure 151/69 mmHg, and oxygen saturation 93% on room air. He was placed in four-point restraints on the resuscitation bed as a precautionary measure because statements by the EMS personnel and LEOs present warned of the difficulty in controlling his violent behavior. The primary survey was notable for rapid, deep breathing consistent with and indicative of compensation for severe metabolic acidosis.

Analysis of the subject's blood for standard resuscitation biomarkers was performed on arrival. The following were of interest in this case: arterial pH 6.70, pCO_2 44 mmHg, and bicarbonate 5 mEq/L (indicating an incomplete respiratory compensation for a severe metabolic acidosis); venous potassium 4.2 mEq/L, creatinine 1.6 mg/dL, lactate 30 mg/dL, troponin I 0.083 ng/mL, and CK 542 units/L; urine drug screen was positive for metabolites of cocaine but did not indicate acute cocaine use.

The patient was nasally intubated and placed on a mechanical ventilator at high minute ventilation in order to more fully compensate for his metabolic acidosis. A repeat arterial blood gas analysis obtained within 30 minutes after intubation showed pH 6.82, pCO_2 34 mmHg, and bicarbonate 5.4 mEq/L. The patient was admitted to the intensive care unit and over the course of the next 48 hours was weaned off of sedation and extubated. His serum biomarkers returned to normal. The troponin I level peaked at 0.213 ng/mL the following day and then normalized. The patient's mental status returned to normal and his psychiatric status was verified to be at baseline by hospital day 2. He had no recollection of the events leading up to his violent behavior and was amnestic to the restraint and sedation event. He did admit to chronic cocaine abuse, but denied use within the previous week. He was discharged from the hospital after 72 hours and his discharge summary listed numerous discharge diagnoses, including profound metabolic acidosis secondary to agitation and cocaine use in the setting of underlying psychiatric disease.

DISCUSSION

The primary purpose for this case report is to add support in the medical literature for what we believe is a novel and effective management solution for severe ExDS. Excited delirium syndrome usually presents first in the prehospital environment. There is literature support to suggest that first-responder rescuers are able to recognize the clinical features of ExDS in the field.[6] As ExDS becomes more recognizable to clinicians, we believe that its mortality will fall as a result of earlier recognition and intervention.

Excited delirium syndrome is a term that has been used for decades to describe a behavioral syndrome that was first described by Bell as a psychiatric syndrome of lethal, febrile, manic behavior seen within some institutionalized patients in the mid-1800s.[7] At the time, it was called "Bell's mania." The work by Bell, as well as that by Wetli and Fishbain, describes a series of subjects who exhibited clinical behavior very similar to our two cases but went on to die suddenly and unexpectedly. Since then, others have used different terminology such as "agitated delirium," "cocaine agitation and psychosis," and "delirious mania" to describe what appears to be the same phenomenon. However, there is recent consensus of the term ExDS in the emergency medicine literature.[4]

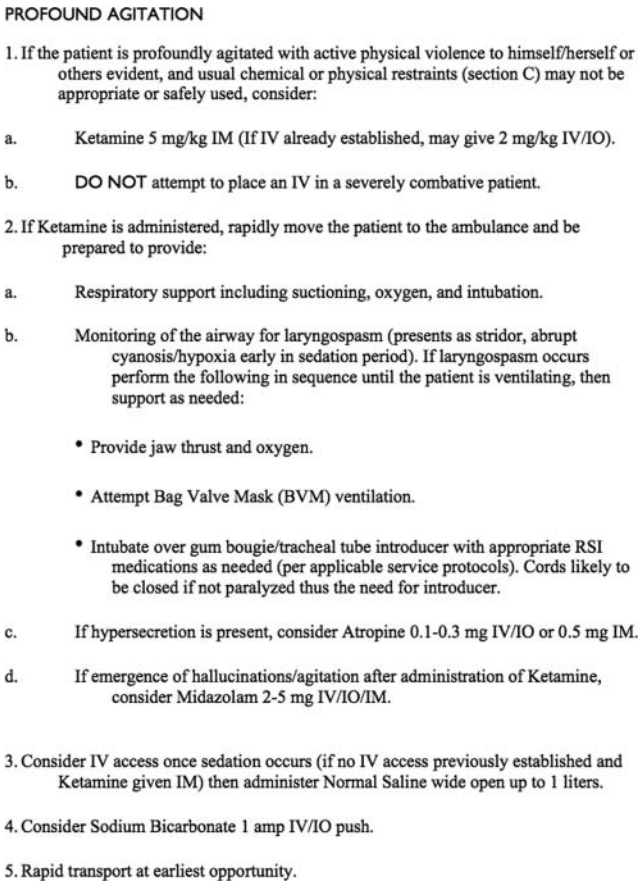
There is little epidemiologic data about ExDS except that it is highly associated with illicit stimulant use, mental illness, and a gender-specific and age-specific risk, as the overwhelming majority of cases in the literature occur in males with a mean age of 36 years.[2,8–10] The severe agitation of ExDS is not seen routinely in cocaine-overdose deaths. Cocaine and cocaine metabolite levels found in the bodies of patients who died of ExDS do not indicate that death occurs from cocaine overdose and suggests a different mechanism of death and a different syndrome.[4] This is consistent with what occurred in our two cases that showed nonacute cocaine metabolites upon toxicology screening of their urine, but did not reveal evidence of cocaine use within the immediate time frame prior to the onset of bizarre behavior. The behaviors seen in an acute ExDS emergency closely resemble delirious, agitated psychosis, and these behaviors are believed to be mediated by an increase in cerebral extracellular dopamine level.[11] This is thought to occur because of downregulation of dopamine transporter protein that allows excess dopamine to persist in the intracellular space causing behavioral change. Mash et al. have demonstrated a lack of dopamine transporter protein activity in persons exhibiting ExDS behavior at or very close to the time of death that supports this mechanism.[12] There is a high association between late-stage ExDS and death due to cardiopulmonary arrest. It is believed that ExDS occurs along a spectrum, starting initially as

odd behavior that may be dismissed by witnesses if unrecognized. If allowed to continue unchecked, ExDS progresses to severe states of agitation, paranoia, and incoherence.[13] The dangerous pathophysiology associated with this acute emergency is believed to be a rapidly worsening metabolic acidosis in addition to significant catecholamine surge that may induce cardiac dysfunction.[14] Both conditions are associated with fear or paranoia-driven violent acts, fleeing from attempts at help or rescue, and significant physical activity usually in the form of resistance to control and restraints.[15] It is likely that because of incoherence, the ExDS subject does not recognize or correctly interpret the normal internal cues of extreme exhaustion and is able to continue his or her vigorous physical activity unabated. This late-stage ExDS behavior is classic, associated with profound acidosis and death, and has been described very well in the literature.[16] Stimulant intoxication may also contribute to worsening of these conditions.[17,18] Recommended treatment of ExDS, especially in later stages, primarily consists of medications with sedating or dissociative properties.[19]

The use of ketamine as a successful dissociative sedative within the hospital has been described in the literature for conditions requiring deep procedural sedation, with minimal complications.[20,21] Ketamine has also been used on trauma patients for agitation control in the prehospital setting.[22] Additionally, there have been case reports of successful use of ketamine in prehospital novel rescue situations to facilitate chemical restraint and extrication.[23,24]

We would caution against using ketamine sedation in situations that do not warrant the immediate need for interruption of the severe, life-threatening, metabolic acidosis/catecholamine surge crisis seen in late-stage ExDS. Clinicians should always consider the risk–benefit ratio of a possible intervention. In 2012, Burnett et al. described a case report of laryngospasm as a complication of prehospital ketamine administration in an agitated person.[25] Laryngospasm is a known potential side effect of ketamine and can cause airway compromise. Although that person was labeled as an ExDS patient, the details of that case (near normal pulse rate of 101 beats/min in the field with a respiratory rate of 18 breaths/min, normothermia, normal CK level, and a negative toxicology screen) make it unlikely to be late-stage ExDS with an immediate threat to life. Late-stage ExDS, where subjects are wildly agitated and violently exertional, should have marked tachycardia, hyperventilation secondary to metabolic acidosis, and hyperthermia with CK derangement. We would advocate that ketamine not be the chemical solution for every unruly or belligerent subjects, as this would lead to overuse with unnecessary risk.

Ketamine has unique properties that make it well suited for use in the prehospital setting. Typical dosing is 1–2 mg/kg intravenous (IV) and 4–5 mg/kg IM. In the prehospital setting, and particularly in ExDS where safety of the rescue personnel can be compromised during the struggle for control and restraint, IM administration is the preferred method, as IV access would be difficult to achieve. When given IM, ketamine has an onset of action of approximately 5 minutes and duration of action of 20–30 minutes. These properties are ideal for interrupting and controlling ExDS in the field. Quickly and definitively sedating a patient with ExDS is crucial to stopping the continued catecholamine surge and metabolic acidosis. The side-effect profile for ketamine includes a low risk of laryngospasm, hypersalivation, nausea, and vivid emergence hallucination reactions. This needs to be considered in the overall risk–benefit ratio of need. Our EMS system standing-order protocol reserves the use of ketamine for profound agitation involving imminent risk of injury to patient or provider (Fig. 1).



PROFOUND AGITATION

1. If the patient is profoundly agitated with active physical violence to himself/herself or others evident, and usual chemical or physical restraints (section C) may not be appropriate or safely used, consider:

a. Ketamine 5 mg/kg IM (If IV already established, may give 2 mg/kg IV/IO).

b. **DO NOT** attempt to place an IV in a severely combative patient.

2. If Ketamine is administered, rapidly move the patient to the ambulance and be prepared to provide:

a. Respiratory support including suctioning, oxygen, and intubation.

b. Monitoring of the airway for laryngospasm (presents as stridor, abrupt cyanosis/hypoxia early in sedation period). If laryngospasm occurs perform the following in sequence until the patient is ventilating, then support as needed:

- Provide jaw thrust and oxygen.
- Attempt Bag Valve Mask (BVM) ventilation.
- Intubate over gum bougie/tracheal tube introducer with appropriate RSI medications as needed (per applicable service protocols). Cords likely to be closed if not paralyzed thus the need for introducer.

c. If hypersecretion is present, consider Atropine 0.1-0.3 mg IV/IO or 0.5 mg IM.

d. If emergence of hallucinations/agitation after administration of Ketamine, consider Midazolam 2-5 mg IV/IO/IM.

3. Consider IV access once sedation occurs (if no IV access previously established and Ketamine given IM) then administer Normal Saline wide open up to 1 liters.

4. Consider Sodium Bicarbonate 1 amp IV/IO push.

5. Rapid transport at earliest opportunity.

FIGURE 1. Hennepin County Emergency Medical Services (EMS) System Advance Life Support Protocols, 2012 edition, Adult Behavioral Emergency. From: Hennepin County Emergency Medical Services System. Advanced Life Support Protocols, 2012 edition. Adult Behavioral Emergencies Protocol, p 68. Available at: http://www.hennepin.us/files/HennepinUS/HSPHD/Public%20Health%20Protection/Emergency%20Medical%20Services/EMS-System%20Policies/System_Policies-Protocols/ALS%20Protocols-Large-Redacted.pdf. Accessed June 30, 2012. Reprinted with permission from the Hennepin County Human Services and Public Health Department, EMS Planning and Regulation Unit, EMS Advisory Council. IM = intramuscular; IO = intraosseous; IV = intravenous; RSI = rapid-sequence intubation.

Other sedatives commonly used for sedation such as benzodiazepines and neuroleptics can be problematic for a number of reasons. Respiratory depression and prolongation of the cardiac QT interval have been described with these medications.[26,27] Both are complications associated with unintended sudden death, and long QT syndrome has been postulated as a possible mechanism of death in ExDS.[28] The need for additional sedation has also been described when only benzodiazepines are used.[29] Since patients with ExDS are well past the levels of agitation seen in those who are simply manic, hallucinatory, belligerent, or intoxicated, controlling them often requires large doses of typical sedatives often involving more than one medication. With increasing doses or multiple medication combinations comes the increased risk of respiratory depression. This is particularly dangerous in this setting because of the respiratory drive needed to compensate for the severe underlying metabolic acidosis. Ketamine keeps protective airway reflexes intact and rarely affects respiratory drive even with increased dosages.[30,31] There is little danger in giving a larger dose of ketamine than is necessary to reach dissociation, as this will only prolong the sedation duration. This makes effective estimation of dosage by prehospital personnel in a dynamic and stressful situation much easier and lessens the need for absolute dosing precision.

We believe that ketamine represents an ideal sedative for use in the setting of ExDS with profound agitation. During extreme anaerobic exertion, high minute ventilation is required to buffer an acidotic condition. Chan et al. showed that physical restraint does not significantly affect ventilation after exertion.[32] However, physical restraint and its true effect on compensatory ventilation is difficult to study for extreme situations and it is unreasonable to physically restrain someone and allow continued exertion against the restraints. Thus, chemical restraint is necessary and needs to be reliable and effective with rapid onset, and possess an acceptable side-effect profile.

CONCLUSION

We have presented two cases that highlight the typical clinical presentation and pathophysiology of severe ExDS. Awareness and prevention of sudden death in ExDS should be a primary concern. Management must be directed at immediate intervention, with the goal of rapid sedation to prevent further agitation, resistance, metabolic acidosis, and catecholamine surge.

The use of ketamine as a sedation agent in the prehospital control and management process appears to offer the excellent combination of rapid onset with a low side-effect profile. It can be easily administered in the prehospital environment with success. This strategy bears further study and surveillance by the prehospital care community for evaluation of side effects and unintended complications.

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The Use of Prehospital Ketamine for Control of Agitation in a Metropolitan Firefighter-based EMS System.

Keseg D, Cortez E, Rund D, Caterino J.

Abstract

INTRODUCTION: Prehospital personnel frequently encounter agitated, combative, and intoxicated patients in the field. In recent years, ketamine has been described as an effective sedative agent to treat such patients; however, a paucity of research exists describing the use of prehospital ketamine. The objective of this study was to provide a descriptive analysis of the Columbus Division of Fire's experience with utilizing ketamine in the prehospital setting. We hypothesized that ketamine administration improves patient condition, is effective at sedating patients, and does not result in endotracheal intubation in the prehospital setting or in the emergency department (ED).

METHODS: We conducted a retrospective cohort chart review of Columbus Division of Fire patient care reports and hospital records from destination hospitals in the central Ohio region between October 2010 and October 2012. All patients receiving ketamine administered by Columbus Division of Fire personnel for sedation were included. Patients 17 years and younger were excluded. The primary outcome was the percentage of patients noted to have an "improved" condition recorded in the data field of the patient care report. The secondary outcomes were the effectiveness of sedation and the performance of endotracheal intubation.

RESULTS: A total of 36 patients met inclusion criteria over the study period. Data were available on 35 patients for analysis. The mean IV dose of ketamine was 138 mg (SD = 59.5, 100-200). The mean IM dose of ketamine was 324 mg (SD = 120, 100-500). Prehospital records noted an improvement in patient condition after ketamine administration in 32 cases (91%, 95% CI 77-98%). Six patients required sedation post-ketamine administration either by EMS (2) or in the ED (4) (17%, 95% CI 6.5-34%). Endotracheal intubation was performed in eight (23%, 95% CI 10-40%) patients post-ketamine administration.

CONCLUSION: We found that in a cohort of patients administered ketamine, paramedics reported a subjective improvement in patient condition. Endotracheal intubation was performed in 8 patients.

KEYWORDS: agitation; ketamine; prehospital

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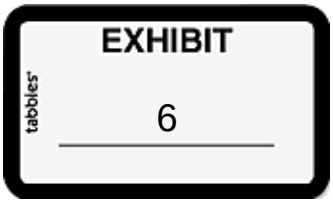

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NOTIFICATION OF ENROLLMENT

Project Title: Ketamine versus Midazolam Prehospital Agitation

You are receiving this form because you or someone you care for was included in a research study examining patients with agitation. This research study is being done to find out if one of two drugs, ketamine or midazolam, is better for treating agitation. Agitation is a state of extreme emotional disturbance where patients can become physically aggressive or violent, endangering themselves and those who are caring for them. The Hennepin EMS System is undergoing a standard protocol change from one drug to the other; to compare which drug may be better the study doctors are collecting data on patients before and after the protocol change. Experts have recommended both drugs for agitation; previous studies from our hospital suggest both drugs have similar risk, but the two have never been compared in the same study at any hospital.

While you were being treated by the EMS personnel, trained research associates monitored your vital signs, such as your heart rate and blood pressure, and wrote down the medications and treatments you received. Data was collected from medical information and blood samples obtained as part of your regular care. In addition, the study doctors may check the medical record to examine what happened during the hospital stay. The study participation and information will be kept completely confidential.

There was no cost to you to participate in this study, and you will not be charged. You will not be paid for your participation. Because this study involves collection of data in a setting where usual care was conducted, you were not consented prior to enrollment. This is permitted under federal regulations for Waiver of Consent Research (45 CFR 46.116(d)).

Your participation in this study will be kept completely confidential. The collected information will be identified only by a number assigned when you entered the study. Participation is voluntary; if you do not want your data used it will be removed.

If you have any questions regarding your participation in this study, please contact Dr. Jon Cole at (612) 873-8791. If you want to talk to someone other than the study doctor, you can call the Office of Human Subjects Research at Hennepin County Medical Center at (612) 873-6882 or write to:

Dr. Craig Peine, MD
Chair, Human Subjects Research Committee
Minneapolis Medical Research Foundation
914 South Eighth Street
600 Fred L. Shapiro Building
Minneapolis, MN 55404

CONSENT FOR CLINICAL INVESTIGATION

EXHIBIT
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OPINION EXCHANGE

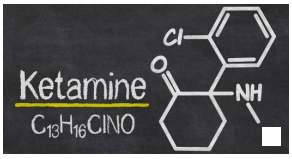
Counterpoint: Discussion of ketamine use on suspects is incomplete

As EMS medical directors in the Twin Cities, we want members of the public to understand all the factors that must be considered — and the care we take in our work.

By Jeffrey Ho , Charlie Lick , John Lyng , Marc Conterato , Paul Nystrom and Kevin Sipprell

JUNE 19, 2018 — 6:00PM

As medical directors of the five advanced life support 911 Emergency Medical Services (EMS) systems operating in Hennepin County, we feel it is important that we respond to recent concerns raised about the use of ketamine in emergencies with law enforcement present (Star Tribune coverage: June 15, 16, 17 and 19; see (http://www.startribune.com/search/?q=ketamine+mannix) tinyurl.com/st-ketamine).



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The use of ketamine, as a safe and effective option for sedating patients in a crisis state in emergencies, is well-documented in medical and scientific literature. Emergency medicine physicians at Hennepin Healthcare are leaders in the research behind safe medical sedation and ketamine use, and our EMS systems are considered national and international leaders in prehospital sedation for agitation. We all are experiencing higher call volume and responding to an increased level of agitation due to the rise in drug abuse and mental health emergencies. The use of ketamine in emergency situations by EMS professionals has saved lives in our local communities and around the world.

The writers of a recent city of Minneapolis draft report suggest that an issue may exist with how medical sedation is provided to patients experiencing serious distress or agitation. The safety of patients is paramount and foremost in the minds of our paramedics as they respond to what are often very dangerous and difficult situations. The decision to use ketamine in a crisis to stabilize an individual is a medical one that is made by the paramedic to prevent injuries and even save a person's life. Sedation is not, and should never be, used as a consequence of a perceived crime, as implied by the draft report. Any patient who receives sedation is transported only to an emergency department as a receiving destination.

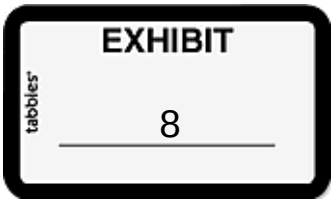
The physical response to a crisis on a person's health and body can be life-threatening. Allowing uncontrolled exertion and agitation to continue can lead to a high-risk situation for the patient called metabolic acidosis — the buildup of waste products in the body. At its most extreme, agitation can become a condition of "excited delirium," which is a life-threatening syndrome recognized by the American Academy of Emergency Medicine and the American College of Emergency Physicians. When left unchecked and untreated, the outcome is often death. Treatment with a sedative is a time-sensitive response.

Of the available sedatives in our EMS system, ketamine is often the best choice based on the patient's behavior, the severity of agitation, the timing, the risk of a patient causing self-injury even after physical restraints have been applied and other medical considerations.

The choice of medical sedation in these challenging situations requires EMS professionals to balance all of the risks and benefits quickly. It is difficult to accurately capture the true state of a patient during an emergency or a behavioral health crisis from only a partial view of the situation. While it may appear that a patient is physically calm at certain points during a crisis situation — even after physical restraints have been applied — the patient may not be fully stabilized and could still be at risk of causing further harm to themselves or others.

As national leaders in emergency medical prehospital care, we are committed to acting in the best interest of the communities we serve and to treating our patients with respect. We understand that the questions raised in this draft report are concerning, and the disparaging statements made by EMS staff and police in no way reflect the values of our local EMS systems and will be addressed. However, the conclusions about ketamine in this draft report were made without consulting medical professionals. Not fully understanding the complex and dynamic decisionmaking by EMS professionals when deciding to sedate someone in a medical crisis can lead to misunderstandings about the circumstances involved. It can also lead to public mistrust of a lifesaving treatment that could hurt the ability of EMS personnel to protect lives in crisis situations.

Therefore, we believe it is critical that an independent review of the use of ketamine is conducted that includes the medical evidence and research in its findings. As EMS professionals who go to work every day to protect lives, we are fully committed to ensuring that our practices are safe and that they meet the standards of care and the protocols that guide us. We are fully committed to working with our public safety partners and providing accurate, verifiable information to the community about how we perform our duties.



Dr. Jeffrey Ho is chief medical director for Hennepin EMS. Dr. Charlie Lick is medical director for Allina EMS. Drs. John Lyng and Marc Conterato are co-medical directors for North Memorial Health Ambulance. Dr. Paul Nystrom is medical director for Edina Fire and EMS. Dr. Kevin Sipprell is medical director for Ridgeview Ambulance.